THE OUTPUT OF THE HEART WITH OBSERVATIONS ON ITS VARIATIONS IN SOME PATHOLOGICAL STATES.

by

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The essential function of the heart is to act as a pump, and the efficiency of a pump is gauged by its output per unit of time. Thus the importance of the quantitative study of the output of the heart has long been recognised. Yet, though physiologists have for many years studied this function both in animals and in man, the difficulties have been such that accurate knowledge has accumulated but slowly. Text books do not yet contain figures relative to the circulation rate, as the output of the heart per minute has been termed, in man at rest or during the various phases of bodily activity. Little wonder, therefore, that the conception of quantitative study of the blood flow has not yet entered, to any large extent, into the clinical field. Yet, were a suitable method of estimation available, the study of circulation rate in disease would yield much valuable information.

This is especially obvious in cardiac disease. The effect of the various types of cardiac lesions on the output of the heart could be definitely determined and their relative severity thus evaluated. Further information regarding the mechanism of cardiac failure/

failure could be obtained and the value of various therapeutic agents used in circulatory disease could be more accurately determined. At present there is no generally accepted and accurate test of the functional efficiency of the heart. If the cardiac output could be measured, such a test could probably be evolved. In myxoedema and hyperthyroidism circulatory changes are to be expected, and by following such cases during treatment interesting facts regarding the relationship of the circulation and the metabolism might be obtained. In anaemias, fevers, and various other pathological states information of value would probably also result from a study of the circulation rate.

Recently a method was introduced by two American workers, Henderson and Haggard of Yale,[1] which they claim is suitable for estimating the circulation rate in patients untrained to respiratory experiments. This method has since been employed by others,(31,32,33,34) in the study of circulation rate in normal individuals. The method has now been applied by the writer to pathological conditions and the results thus obtained are the basis of this thesis.

Since there is as yet no generally accepted opinion regarding the average circulation rate in normal individuals, and the extent of its variation under varying physiological conditions, a resumé of the/

the work done on the subject will first be given. What little work has already been done on circulation rate in pathological states will then be reviewed, before the results of the present investigation are set forth and discussed.

THE CIRCULATION RATE IN HEALTH.

Direct Measurement in Animals.

For the direct measurement of cardiac output in animals it is necessary either to determine the exact amount of blood passing through the aorta in a definite period of time, or to measure the change produced in the volume of the ventricle with each systole. If the first method be used the Circulation Rate (C.R.) is determined primarily and this divided by the heart rate will give the output per beat or Stroke Volume (S.V.). With the second method the S.V. is directly determined and the C.R. got by multiplying by the heart rate.

For direct measurement of the flow through the aorta, the Stromuhr was used by the Ludwig school of Physiologists and others towards the end of last century. The results obtained were very variable and indicated a small cardiac output. The difficulties in Stromuhr measurement combined with the shock associated with the extensive operative procedure necessary, greatly reduce the value of the results obtained by this method.

One observer, Stolnikow[2] at this period, tied off the branches of the aorta confining the outflow to one axillary artery, the blood flowing from this being measured/

measured and returned into a vein. This method is interesting in that it foreshadows the more recent heart-lung preparation. The results obtained indicate in dogs S.V.s. varying between .32 and 1.6 cc. per kilo body weight, with an average of under .64 cc. per kilo.

The earlier workers, using plethysmographic methods, enclosed the whole heart in the instrument. Changes in volume in both auricles and ventricles were therefore recorded, making the results very difficult to interpret.

By modifications of these methods more recent workers have made many important observations. Notably Yandell Henderson, using a plethysmographic method, and Starling and his co-workers, who measured the blood flow directly in a modified circulation.

Henderson (3,4,5 & 6) in his experiments used dogs under morphine and ether anaesthesia. The volume changes in the ventricles were recorded by means of a simple cardiograph which enclosed the exposed ventricles, fitting closely round the auriculo-ventricular groove. Air movements resultant on changing ventricular volume were transmitted from the cardiograph box through a tube to a tambour and recorded on a moving drum. Artificial respiration or spontaneous respiration of air under pressure was employed, and an endeavour made to lessen shock by maintaining/

maintaining a sufficiently high alveolar CO_2 tension.

The volume curve of the ventricles thus obtained was found, when the heart was beating slowly but vigorously, to consist of a rapid rise at the beginning of diastole, a plateau, and then a sharp fall with systole. In these circumstances auricular systole produced no significant effect on the ventricular volume. From the form of the ventricular volume curve the cardiac cycle was divided by Henderson into three phases, - systole - , followed by a rapid filling of the ventricles to their maximum, - diastole -, followed by a period lasting up to the next systole

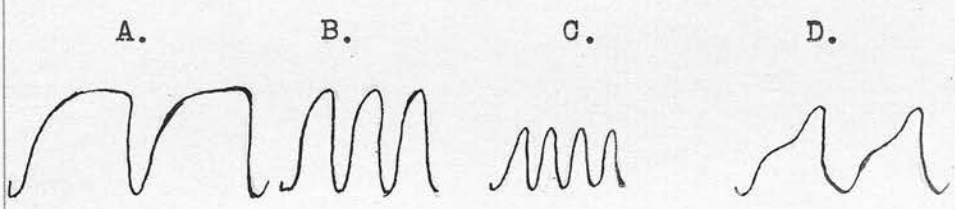

Fig. 1. Ventricular Volume Curves (diagramatic).

A. Vagal Beats.
B. Optimum Heart Rate.
C. Rate above Optimum.
D. Venous Pressure below the Critical Level.

during which there was no appreciable increase in ventricular volume, - diastasis -.

With more rapid heart rates diastasis was found to diminish in length until a rate was reached when systole immediately followed diastole. Thereafter further increase in heart rate resulted in a pro-

gressive/

progressive shortening of the diastolic upstroke necessarily associated with a corresponding shortening of the systolic downstroke.

On examining the curves from such a heart, obtained at various rates; it was found that the curves of diastolic filling, though possibly varying in length, were all superimposable the one upon the other, i.e. were all arcs of the same circle. Similarly all the systolic curves were arcs, varying in length, of a common circle.

Relaxation or diastolic filling and contraction or emptying of the ventricle appeared therefore each to have an inherent rate which was not affected by changes in the heart rate. From this it was concluded that the stroke volume was at its maximum when the heart was beating slowly, that as the heart rate increased the circulation rate increased proportionately up to a certain optimum pulse rate at which a full diastole was immediately followed by systole with no intervening period of diastasis. At higher rates the C.R. would not increase in direct proportion to the increase in heart rate since the S.V. was now diminishing. At still higher rates diminution in S.V. would be such that the C.R. would also commence to diminish, the ultimate result, if the heart rate continued to increase, being a condition approaching cardiac tetanus.

On making simultaneous records of the venous pressure/

pressure it was found that such results were obtained when the venous pressure was equal to 50 mm. H_2O, which, according to Henderson, is the usual venous pressure in the resting dog. If the venous pressure was raised above 50 mm. H_2O by transfusion and pressure on the abdomen no alteration was induced in the form or height of the ventricular volume curve. Such a rise in venous pressure presumably occurs in the intact animal during exercise. If however, the venous pressure were reduced by bleeding the animal, a different type of curve was obtained (fig 1D.). Even at slow pulse rates ventricular filling was now shown to be occurring from the end of one systole to the beginning of the next, and auricular systole produced a definite increase in ventricular volume. The curves obtained at different heart rates were not superimposable. From these results Henderson concluded that the stroke volume is at its maximum at the normal venous pressure and cannot be increased by increase in venous pressure. At venous pressures below normal, such as might occur in circulatory shock or post-haemorrhagic conditions, the stroke volume is a variable quantity.

The magnitude of the stroke volumes indicated by these experiments as occurring in the healthy dog at rest is 1.5 - 2 cc. per kilo.

From these results it would appear that, in the healthy/

healthy individual the stroke volume is a constant function as large with the individual resting as while he is doing muscular work, any increase in circulation rate being due entirely to increase in pulse rate.

Starling and his co-workers (7,8,9 & 10) a few years later, found that the behaviour of the heart in the heart-lung preparation, suggested very different conclusions from those arrived at by Henderson. In the heart-lung preparation the systemic circulation is replaced by a system of tubes into which the blood passes through a cannula inserted into the aorta and from which it flows again into the right side of the heart through a cannula in the superior vena cava. The system is so adapted that the arterial resistance, the venous inflow, and the temperature of the circulating blood, can all be varied and the cardiac output, arterial and venous pressures, measured. Artificial respiration is maintained and, since the pulmonary circulation is intact, the heart is kept supplied with oxygenated blood. In Starling's work dogs were the experimental animals.

It was first shown[7], that the rate of the heart in such a preparation varied directly with changes in the temperature of the circulating blood. Such changes in rate were found to have no effect on the cardiac output. Increase in the arterial pressure resulting from increased peripheral resistance caused

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a slight diminution in the output, but this diminution was shown[8] to be proportional to the increase in coronary circulation resultant on the raised arterial pressure. The actual output of the ventricle therefore remained unchanged even though the arterial pressure were increased.

On increasing the rate of flow into the right heart, the output was found to increase to an exactly corresponding extent. This correspondence of output to venous inflow was found to hold almost absolutely so much so that in succeeding experiments the output alone was measured. In these experiments the Central Nervous System being functionless, there is no nervous control of the heart. Changes in rate depend, therefore, on changes in the temperature of the circulating blood and the correspondence of inflow to output can only be brought about by extensive changes in the stroke volume. Variations in stroke volume from 1.69 to 13.9 cc. and 4.42 to 22.3 cc. in hearts of 44 and 56 G. weight are typical examples found in the protocols of these experiments.

In a further series of experiments the correlation between arterial pressure, venous pressure, heart rate, and venous inflow (this being taken as equal to output) was investigated. It was shown that with a small inflow the venous pressure might be zero. With increased inflow the venous pressure did not increase markedly so long as the inflow was not sufficient to

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cause more than a minimal distension of the relaxing ventricles. As the inflow increased further, however, a definite positive pressure was present throughout diastole. When the inflow reached its maximum, i.e. filled the ventricles to their utmost capacity during diastole, the venous pressure was usually found to be between 200 and 250 mm. H_2O. Increase beyond this optimum venous pressure, if maintained, resulted in lung oedema.

It appeared, therefore, that increase in venous pressure increased the rate of filling of the heart. In one experiment, with the venous pressure at the optimum, a heart of 56 G. pumped as much as 3 litres of blood per minute. On increasing the arterial resistance it was found that, though the output, and consequently the inflow, remained the same, the venous pressure rose. It was concluded therefore that the higher the arterial pressure the sooner would the optimum venous pressure be reached and the smaller would be the maximum output.

When the inflow was maintained constant and the heart rate increased; the venous pressure fell, the output of course remaining constant. When, however, an attempt was made to keep the venous pressure constant with a rising pulse rate the output increased, for to maintain in these circumstances a constant venous pressure, it is necessary to continually increase the inflow.

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From this it appeared that the more rapid the heart rate the greater could the inflow be without the venous pressure increasing beyond its optimum.

In other words a heart beating rapidly can continue to discharge a maximum amount of blood at each systole provided the venous inflow is of sufficient volume. The maximal dilatation of the heart, it is suggested by Starling, is determined in the intact animal by the non expansile pericardium.

It was noted that towards the end of an experiment, when the heart was presumably becoming fatigued, with a constant inflow, the venous pressure gradually rose and the diastolic filling increased, the output remaining constant. These signs of fatigue might be noted first in one ventricle only.

On these various findings Starling formulated his well known "law of the heart" viz.- within physiological limits the larger the stroke volume of the heart the greater are the extent of its contractions and the amount of chemical change at each contraction. In other words, the energy of contraction however measured is dependent on the length of the muscle fibres. On this assumption cardiac contraction is essentially the same as the contraction of voluntary muscle. If this be accepted then the output is constantly equal to the inflow because the strength of the contraction varies with the ventricular filling.

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The uniformity of stroke volume maintained against increasing arterial resistance could be explained by assuming that the output from the first few beats is diminished, and the consequent increased filling of the heart provokes a greater power of contraction. The increasing dilatation noticed towards the end of an experiment would depend on the fact that the muscle was becoming fatigued, and increased dilatation was necessary to give rise to a contraction sufficiently powerful to maintain the output.

It would appear from the above that under the experimental conditions prevailing, the stroke volume of the heart is a variable function, the variation being chiefly dependent on the venous inflow and pressure. Yet though in these experiments the stroke volume of the heart could be made to vary, and great increase in the output per minute could be produced, they provide no information as to whether, in the intact animal, the stroke volume actually does vary or the circulation rate increase to the extent indicated as possible; nor can the usual output of the heart in the intact animal be inferred from them.

METHODS OF ESTIMATING THE CIRCULATION RATE BASED ON THE FICK PRINCIPLE.

As early as 1870 Fick[11] pointed out that, if the oxygen contents of the blood in the left and in the right sides of the heart were known and the oxygen absorbed per minute were also known, the circulation rate could be calculated according to the equation

$$C.R. = \frac{O_2 \text{ cons. per min.}}{\text{Art } O_2 - \text{Mixed Ven } O_2}$$

Thus if 250 cc. of O_2 are consumed per minute it is evident that these 250 cc. are carried away by the blood passing through the lungs. If now the arterial blood contains O_2 amounting to 185 cc. per litre and the mixed venous blood in the right side of the heart contains only 135 cc. per litre, each litre of blood passing through the lungs must carry away 50 cc. of O_2. Therefore the circulation rate through the lungs must be 5 litres per min. $(\frac{250}{50})$

The circulation rate through the lungs is, of course, the same as the systemic circulation rate. Were it otherwise the heart would manifestly come to a standstill. The same principle applies to CO_2 thus

$$C.R. = \frac{CO_2 \text{ output per min.}}{\text{Mixed Ven. } CO_2 - \text{Art } CO_2.}$$

Fick, /

Fick, though suggesting this principle, did not himself use it in any actual determination of the circulation rate. It was first employed apparently about 1886 by Grehant and Quinquand[12] working on dogs. They found C.Rs. varying from 512 - 2164 cc. in dogs of from 7 to 18 kilos.; no pulse rates were given.

The most important early work, however, in which the Fick method was employed is that of Zuntz and Hagemann[13]. Using unanaesthetised horses in their experiments they obtained samples of blood from an artery and drew off mixed venous samples from the right auricle through a sound passed down a jugular vein. They were able to make determinations both while the animals were at rest and at work. The average circulation rate for the best ten experiments on animals averaging 347 Kg. was, during rest, 29 litres per min. and during moderate work 53 litres per min. They made no actual counts of the heart rate but assumed this to be 40 at rest and 55 during such work as was performed. The average stroke volume was therefore taken to be 729 cc. during rest, and 964 cc. during work, or 2.09 cc. per kilo body weight at rest and 2.77 cc. per kilo at work. The difference between arterial and mixed venous oxygen in these experiments was at rest 7.44 vol. and during work 9.34 vol. indicating an increase in oxygen utilization during work. The average stroke index, i.e. stroke/

stroke volume per kilo. of body weight, is in the same range as the stroke index later found by Henderson in dogs. The authors, however, were of the opinion that the stroke volume increased during work although absence of actual counts of the heart rate renders these results indeterminate on this point. The object of the experiments was to estimate the work performed by the heart, and for this purpose the actual heart rate is not essential.

With the introduction of new methods of blood gas analysis, the estimation of the circulation rate by the Fick method has been made simpler and more accurate. In 1919 Barcroft and his collaborators[14] using an improved technique found in 43 experiments on 21 unanaesthetised healthy goats an average C.R. of 3.67 litres per min. or 133 cc. per kilo body weight. The heart rates are not given in the protocols of these experiments. The average arterio-venous oxygen difference was found to be 5.83 vol.% . No definite influence of weight or sex on the C.R. was evident.

More recently E.K. Marshall[15] employed a similar technique with unanaesthetised dogs, making repeated determinations on 5 animals - 2 males and 3 females. The C.R. in the males, determined in one case repeatedly over a period of two years, remained remarkably constant. In the females variations up to 40% occurred. The author suggests that these variations were/

were due to some extent to increase in the C.R. occurring during oestrus. Spontaneous changes in the pulse rate were without effect on the circulation rate of the resting animals except in one female which was pregnant. In the pregnant animal spontaneous increase in heart rate increased the C.R. while the S.V. remained constant. In the other animals the S.V. varied inversely as the pulse rate. The stroke index was in the males constantly above 1, usually about 1.7, the variation being due to changes in pulse rate. In the females the stroke index varied from .68 to 2.08. The arterio-venous O_2 difference was usually between 4 and 5 vols.% but variations in the same animal of from 4.15 - 7.74 vol.% were noted.

There are numerous other instances in recent literature of direct application of the Fick principle in the determination of the C.R. in animals both anaesthetised and unanaesthetised, the circulation usually however being modified in some way for the purposes of the experiment.

Direct application of the Fick principle to man has been attempted, the venous blood being obtained from a cubital vein. Means and Newburgh[16] among others suggested this procedure. It has been clearly shown, however, that the gaseous content of blood from a peripheral vein, is not necessarily the same as that of mixed venous blood from the right heart.

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This method is therefore invalid. Along other lines, however, the Fick principle has been applied much more successfully to the determination of the C.R. in man.

It was evident that, if the air in the lungs could be brought into tension equilibrium with the venous blood and samples of this air obtained and analysed, actual samples of mixed venous blood would be rendered unnecessary. This problem was first tackled by passing a catheter down the trachea and into the right bronchus so as to entirely block the bronchus or one of its larger branches. The air in the portion of lung thus shut off came into equilibrium with the venous blood and samples could be drawn off through the catheter[17]. Plesch[18] introduced a simpler method of obtaining "virtual venous air". He showed that by breathing back and forth into a small rubber bag for 15 - 20 secs. the partial pressures of the gases in the bag, in the lungs, and in the venous blood, could be brought into equilibrium.
The manoeuvre must be completed before one full circulation of the blood has occurred or the venous CO_2 will rise.

The method of calculating the gaseous content of the mixed venous blood in man from respiratory data was put on a firmer basis by Christiansen, Douglas and Haldane,[19] who worked out the CO_2 dissociation curve in man and demonstrated the mutual interaction/

interaction of CO_2 and O_2 in the blood. They also described a method of estimating the circulation rate in man.

Samples of alveolar air were obtained in the ordinary way and the respiratory exchange was measured by the Douglas bag method. The virtual venous air was obtained as follows. 60 - 70 litres of a gas mixture containing roughly the percentages of CO_2 and O_2 expected in the virtual venous air is made up in a Douglas bag. The subject exhales deeply, inhales from the bag and then exhales to the air. This is repeated three times within 15 secs., the last exhalation being into a Haldane-Priestley alveolar air sampling tube. This expiration is stopped after about 1500 cc. have been exhaled and a sample taken. The expiration is then continued to a maximum and a further sample taken. If the CO_2 and O_2 tensions in these two samples remain constant then the gas mixture chosen is in equilibrium with the mixed venous blood. In practice it is usual to start with a CO_2 tension below that expected, and then to use one above, and to reduce the straddle until the correct result is arrived at. By applying this CO_2 tension to the appropriate dissociation curve the CO_2 content of the mixed venous blood is obtained. The arterial CO_2 is in a similar way obtained from the CO_2 tension in the alveolar air. In 1922 Douglas and Haldane[20] published

results/

results obtained by this method. In one subject they found the circulation rate, the subject being under basal conditions and lying flat, to be 7.56 L per min. the S.V. 135 cc. and the Art. Ven. O_2 difference 3.1 vols%. On sitting up these values were little affected. Working on a bicycle ergometer the C.R. rose to 18.76L per min., the S.V. however remaining at 136 cc. The O_2 consumption during this experiment was 1924 cc. per min. and the A.V. O_2 difference rose to 10.6 vols.%. In all experiments on this subject the increase in C.R. during muscular work was directly proportional to the increase in heart rate, the S.V. remaining constant (c.f. Henderson's conclusions from his volume curve experiments). In two other individuals rather different results were obtained. In one at rest sitting C.R. was 5.86L per min., S.V. 76 cc. and A.V. O_2 difference 5.3 vol%. At work with an O_2 consumption of 1348 cc. per min. C.R. was 14.4L per min., S.V. 129 cc. and Art. Ven. O_2 difference 9.4 vol.%.

In the other at rest sitting the C.R. was 4.76L per min., S.V. 67 cc. and A.V. O_2 diff. 5.9 vol.% while, when at work on the ergometer with an O_2 consumption of 1653 cc. per min., C.R. was 15.56L per min., S.V. 152 cc. and Art. Ven O_2 diff. 10.7 vol.%. From these observations it was concluded that in some men the S.V. remains constant during rest, moderate, and/

and hard muscular work, while in others the S.V., being at a lower level during rest, increases during muscular work. It was also concluded that, since the Art. Ven. O_2 diff. or oxygen utilization increases, the increase in circulation rate during work is not proportional to the increase in metabolism unless when the work is so severe that the limit of oxygen utilization has been reached.

In 1917 Henderson and Prince[21] reintroduced the Plesch bag as a method of obtaining virtual venous air.

In their procedure the subject inspired from a 2 litre bag containing expired air, held his breath for 10 seconds, and then exhaled into the bag. This procedure was repeated with suitable intervals of ordinary breathing until samples from the bag showed a constant CO_2 tension. Meakins and Davies[22] modified this procedure by making their subject re-breathe for two respirations into the bag and thus received a better mixing of the air throughout the system, consisting of the alveoli air passages and bag. The CO_2 tension thus obtained was applied to the CO_2 dissociation curve for that individual and the CO_2 content of the mixed venous blood arrived at. The arterial CO_2 was got either by calculation from the alveolar CO_2 tensions or by direct analysis of blood obtained by arterial puncture. The results

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of five determinations by this method on four normal subjects are given. In these subjects the C.R. varied at rest between 7.3 and 8.4L per min. and the S.V. between 100 and 130 cc. In one subject, who at rest had a C.R. of 7.75L per min. with a S.V. of 121 cc. and a CO_2 output of 217 cc. per min., a determination was made while at work on a bicycle ergometer. The CO_2 output rose to 1104 cc. per min. and the C.R. to 17.25L per min., the S.V. however remaining constant at 122 cc. The increase in C.R. here appeared to be due entirely to the increase in pulse rate which occurred.

Burwell and Robinson[23] obtained virtual venous air in a somewhat similar manner, the subject however filling his lungs with a gas mixture of approximately the CO_2 and O_2 tension expected in mixing venous blood before his first expiration into the bag. Instead of calculating the arterial and mixed venous CO_2 and oxygen content from the tensions of these gases in the appropriate air samples, these air samples were brought into equilibrium with samples of the patient's blood in a tonometer and a blood gas analysis then done. This is considered by these authors to be more accurate than using dissociation curves whether standard or individual. The circulation rates of eleven normal adult males were determined by this method, each determination being done with the/

the patient in a semi-reclining position (on a hospital chair) after thirty minutes rest and a fast of twelve hours. In this series the C.R. varied from 3.5 litres per min. with a S.V. of 58 cc. to 6.86 L per min. with a S.V. of 103 cc., the average C.R. being 4.65 per min. and the average S.V. 73 cc. The average oxygen utilization was 5.1 vol.% and the average stroke index 1.1 cc. In one subject whose C.R. was estimated at intervals throughout a year, remarkably constant figures were obtained, the C.R. remaining between 3.7 and 3.96 L per min. and the S.V. between 55 and 60 cc. In another subject, however, who was followed for three months, the C.R. varied from 4.54 L per min. with a S.V. of 73 cc. to 6.78 L per min. with a S.V. of 103 cc. There was no apparent cause for the variations in this subject, - they were not due to variations in metabolic rate. No relationship between C.R. or S.V. and weight, surface area, or metabolic rate was apparent in this series.

Field, Bock and their collaborators[24] further developed and simplified the application of the Fick principle to the study of circulation rate in man. They used an apparatus so constructed that a patient breathing through the mouth-piece could be connected in succession with the outside air, a Haldane-Priestley alveolar air tube and a Plesch bag. During an estimation the patient first breathes to the outside air and accustoms himself to the apparatus. At the end

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of an ordinary expiration he is connected with the Haldane-Priestley tube, the expiration carried to a maximum and an alveolar sample taken. He is then connected with the Plesch bag and rebreathes its contents (a mixture consisting of 6% CO_2 and 94% O_2) 4 - 5 times within 15 seconds. A sample is then taken from the bag.

This whole procedure is repeated at suitable intervals until the CO_2 content in the bag remains constant during two periods. From the CO_2 contents of the alveolar and virtual venous airs thus obtained the tensions are calculated and these applied to a standard CO_2 dissociation curve for oxygenated blood and the CO_2 difference obtained. This method improves on the others in that the alveolar and virtual venous samples are obtained almost simultaneously while the high percentage of O_2 in the rebreathing mixture insures a complete oxygenation of the blood. In these determinations the CO_2 elimination was calculated from the O_2 absorption measured by a Benedict Portable Metabolism Apparatus, a constant R.Q. of .81 being assumed. By this method the circulation rate was estimated in 18 normal young adults - 15 males and 3 females -, all estimations being done with the subject lying and under basal conditions. The results obtained are given in Table 1.

Subjects.		C.R. Litres per min.	S.V. cc.	S.I. cc. per Kilo	Art.Ven. O_2 diff. Vols %
Males	Average	6.95	116 cc	1.67 cc	2.89
15 cases	Highest	10	135 "	2.08 "	1.93
	Lowest	4.49	70 "	1.03 "	4.02
Females	Highest	7.46	120 "	2.31 "	2.16
3 cases	Lowest	5.13	86 "	1.53 "	3.08

TABLE 1. Prepared from the Results obtained by Bock and Field in Normal Individuals (recumbent).

S.I. = output per beat per kilo body weight.

In the majority of cases the stroke index was between 1.5 and 2 cc. In five cases it was lower and in four it was higher. In four cases the stroke volume was so small that a constant S.V. on exertion appeared to the authors impossible for these cases. In the remainder of the cases a constant stroke volume appeared possible. When repeat observations were done on the same subjects, reasonably close results were obtained except in a few individuals in whom variations of several litres were noted although the conditions were similar. These variations were thought by the authors to be real and not the result of experimental error.

Later using the same method these authors made some very interesting observations on the effect of posture on the blood flow.[25] Ten subjects were used, 13 determinations being made with the subjects sitting and/

and 9 with them standing, each being compared with a previous determination with the subject recumbent. The average figures obtained are given in Table 2. A diminution in C.R. was observed in every case on changing from the recumbent to the sitting positions, and in one case only was this fall less than 500 cc.

Lying.			Sitting.			Standing.		
P.R.	C.R.	S.V.	P.R.	C.R.	S.V.	P.R.	C.R.	S.V.
63	8.04	1276	65	6.11	94	90	4.01	44.6
% recumbent value			103	76	74	143	50	35

TABLE 2. Effect of Posture. (from results of Field & Bock)
Average results from 10 subjects - 8 males & 2 females

The fall in stroke volume is even more striking than the fall in C.R. since, especially when standing, there is a marked increase in the pulse rate over the recumbent value. The authors point out that the values obtained in their subjects when sitting correspond fairly closely with the figures given in Burwell and Robinson's series where the subjects reclined in a hospital chair.

MEASUREMENT OF THE CIRCULATION RATE BY MEANS OF FOREIGN GASES.

It would appear an advantage in measuring blood flow to use a gas whose solubility in blood would be constant under all bodily conditions rather than carbon dioxide or oxygen for which the capacity of the blood varies. The first important attempt along these lines was made by Krogh and Lindhard[26] in 1912 using nitrous oxide. This gas has a coefficient of solubility in blood of 0.43, and in the concentration and amount used does not exert any apparent pharmacological action. In an air mixture it can be analysed in a Haldane gas analysis apparatus modified so that the nitrous oxide can be combusted in an atmosphere of hydrogen. In the determinations of C.R. by this method the subject takes a deep inspiration from a recording spirometer in which there is a gas mixture containing 10 - 25% N_2O and 20 - 25% O_2. The breath is held for several seconds, then about 1500 cc. is expired and an alveolar sample taken. After a further interval the expiration is carried to a maximum and a further alveolar sample taken. The amount of air leaving the lungs and the time interval between the taking of the two alveolar samples are got from the spirometer record. Since it is necessary to know the total amount of air in the/

the lungs between the taking of samples, the volume of residual air has to be estimated in each subject. The metabolism is determined by a separate respiratory experiment either before or after the circulatory experiment. The alveolar samples are analysed for CO_2, O_2 and N_2O. From these data the C.R. is calculated. The N_2O absorbed is equal to the difference between the N_2O contents of the two samples multiplied by the volume of air contained in the lungs between the taking of the samples. The mean of the two N_2O estimations multiplied by .43 (coeff. of solubility) gives the N_2O content of the arterial blood. By dividing the first of these by the second the amount of blood passing through the lungs between the taking of the two samples is obtained, and from this the circulation rate per min.

The rate of O_2 absorption during the circulatory experiment is usually found to be higher than the O_2 consumption during the respiratory experiment. This Krogh and Lindhard consider to be due to an increase in circulation rate caused by the manoeuvres necessary in the circulatory experiment, and they make a correction for it. Thus if the estimated C.R. be 4L per min. and O_2 is absorbed during the circulatory experiment at a rate of 300 cc. per min. and during the respiratory experiment at 200 cc. per min., then the corrected C.R. is $4 \times \frac{2}{3}$ or 2.67 litres per min.

This/

This correction, as the following figures show, is frequently very large, and totally alters the order of magnitude of the figures obtained by the N_2O method for the resting circulation rate. The unreduced figures as calculated directly from the observations are placed above the "corrected" figures.

Observed	8.8	10.3	9.5	9.7	7.7	7.9	9.0	7.0
Corrected	7.4	8.55	7.9	6.5	5.6	5.7	4.2	3.0

This correction has been questioned by Douglas and Haldane[27] among others. They attribute the apparently high O_2 absorption during the circulatory experiment to an incomplete mixing of the gases in the lungs; the first alveolar sample containing more of the gas mixture with its relatively high O_2 content.

A large number of estimations have been made by Krogh and Lindhard, using the nitrous oxide method. Their results during rest are lower than those obtained by other methods, the resting C.R. varying between 2.8 and 8.7 litres per min. During work the maximum C.R. observed was 21.66 per min. During rest S.V.s varying from 39 to 103 cc. were observed, while during work the maximum was 116 cc. A definite increase in O_2 utilization was noted to occur during work.

In 1913 Lindhard[28] for the first time made observations on the effect of change in posture on the cardiac output. He found that in the standing position there was, as compared with the sitting, a slight/

slight diminution in the C.R., an increase in pulse rate and, consequently, a considerable decrease in stroke volume amounting in four cases to 20.8%. Females in the recumbent position showed an increase in C.R. of 17.2% and in S.V. of 31% over sitting values. No such change was observed in the male.

In 1918 Lindhard[29] made a statistical survey of the results obtained in normal persons at rest. Thus in seven series of experiments on different male subjects the average C.R. was 5.27L per min. the highest individual average being 6.1L and the lowest 4.15L. In five series on female subjects the average C.R. was 3.65L per min., the highest individual average being 4.3L and the lowest 3.5L per min. All the estimations were done with the subjects sitting.

Boothby[30] reported a series of 61 determinations by the nitrous oxide method on one individual, a healthy adult male, at rest both lying and sitting, and at varying amounts of work on a bicycle ergometer. His results are averaged in table 3. In this individual the increase in stroke volume during work was small, the increase in circulation rate being almost proportional to the increase in pulse frequency. Changing from the sitting to the recumbent position had no apparent effect on the circulation in this man. A very definite increase in oxygen utilization

during/

Oxygen Consumpt. cc. per min.	C.R. Litres per min.	Pulse Rate.	S.V. cc.	Art. Ven. O_2 diff. Vols. per cent.
175	3.37	58	58	5.2
185	3.57	58	62	5.2
320	5.06	75	72	6.3
448	5.30	87	61	8.5
559	6.54	86	68	8.5
608	7.59	91	83	8.0
912	9.31	133	70	9.8

TABLE 3. The Effect of Exercise on the Circulation. Prepared from Boothby's results.

during work is indicated in the last column of table 3.

Means and Newburgh[16] also employed the nitrous oxide method. In two normal male subjects lying at rest, they found the average C.R.s to be 4 and 4.5 L per min. and the average S.V.s 57 and 61 cc. In the first of these the circulation rate increased during work on an ergometer up to 16.9L and the stroke volume to 120 cc. The oxygen utilization did not appear to increase markedly during work in this subject.

All the methods of determining circulation rate in man so far described, require active and fairly extensive cooperation by the subject in the secural of the air samples. The necessity for training the subjects in the technique renders these methods unsuitable/

unsuitable for extensive clinical use. Many cardiac patients, especially if failure is at all marked, find the necessary manoeuvres impossible.

In 1925 Henderson and Haggard[1] introduced their Ethyl Iodide Method in which no cooperation on the part of the subject is required beyond breathing through a mouthpiece and valves for ten minutes. Ethyl iodide is an easily volatilized liquid with, in its gaseous form, a coefficient of solubility in blood of 2 and, according to Henderson and Haggard, possessing the further virtue of being quickly decomposed in the blood, so that in the concentration and amount used, little or none completes one circulation and returns in the venous blood. If then the amount of ethyl iodide absorbed per minute (A) is known and also the amount in each litre of blood passing through the lungs (B) the circulation rate per minute will be $\frac{A}{B}$. To determine these factors the subject breathes through a mouthpiece and valves from a spirometer, charged with a suitable concentration of ethyl iodide in air, for ten minutes. Samples of the inspired, expired, and alveolar air are taken, the alveolar sample being obtained by a new automatic method.

The calculation then is

$$\text{C.R. per min} = \frac{(\text{E.I. in insp. air} - \text{E.I. in exp. air}) \times \text{vol. air breathed}}{\text{E.I. in Alv. air} \times 2\ (\text{coeff. sol.}) \times 10.}$$

Henderson/

Henderson and Haggard in their original paper publish results obtained in three small groups of normal individuals, and these results are condensed in table 4. No attempt was made to secure basal conditions and the period of rest before a determination was only ten minutes. This series shows a higher

Subjects	Position	C.R. Litres per min	S.V. cc.	S.I. cc.	A.V. O_2 diff.
University Athletes Male. 4 aet 22-24	Lying	10.11	153	1.97	3.6 vol%
Sedentary Workers. Male.	Lying (3)	8.86	136	1.86	3.7 vol%
6. 31-35 years.	Sitting (6)	8.06	112	1.56	3.8 vol%
Women. 5. 17-50 years.	Sitting	7.33	92	1.42	4.1 vol%

TABLE 4. Prepared from the Results of Henderson and Haggard; Ethyl Iodide Method.

value for the circulation rate in the resting condition than any other hitherto noted. Insufficient rest and the small number of determination in each subject probably account in part for this high value. Determinations during work were made on several of the subjects. There was in all cases a definite increase/

increase in circulation rate, with in most cases some increase in the stroke volume, though this never amounted to appreciably more than 100% of the resting value. There appeared to be a definite increase in oxygen utilization during work. In one of the athletic subjects 1500 Kg. metres of work per minute was performed with an O_2 consumption of 4600 cc. per min. The C.R. rose to 30 L per min. with a S.V. of 197 cc. The Art. Ven. O_2 difference was therefore apparently 15-16 vol.%. The resting values given for this subject are extremely high, C.R. 14.3 L and S.V. 286 cc.; they have not been included in the table given.

Mobitz[31] using this method reports, in a series of 35 normal men 20-47 years old and weighing 50-100 Kgs., stroke volumes varying between 100 and 163 cc. with an average of 120 cc., the subjects being at rest lying. In 15 women lying at rest the stroke volume varied between 75 and 100 cc. The decrease in the C.R. when determined with the subjects sitting was 20-30% of the recumbent values. During work the stroke volume was found to increase but not to more than twice the resting value. This author has published his results as averages only.

A series of determinations was done on a group of eleven healthy women between the ages of 19 and 25 by Cullis, Rendel and Dahl[32] (Table 5). These determinations/

determinations were made 1-1½ hours after a light breakfast, the subject being in a semi-recumbent position and having rested at least 30 minutes.

	C.R. L per min.	S.V. cc.	S.I. cc. per Kilo.
Average	7.5	100	1.67
Highest	10	126	2.0
Lowest	5.1	70	1.15

TABLE 5. 11 women 19-25 years old. 57 determinations. From the Results of Cullis, Rendel and Dahl.

Fairly wide variations were observed in individual cases even when conditions were apparently similar. Thus in one subject the average of 10 determinations was 7.18 L per min. with a S.V. of 108 cc., while the maximum was 9.2 L and 144 cc. and the minimum 6.80 L and 88 cc.

Davies and Gilchrist[33], in a series of 118 determinations on 18 individuals, made their observations with the patients either lying or sitting after varying periods of rest, and at varying intervals after food, no attempt being made to secure uniform conditions.

Those determinations done on male subjects in a recumbent position have been averaged (table 6), the resultant figures being considerably lower than those given by Henderson or by Cullis.

TABLE 6./

	C.R. L per min.	S.V. cc.	S.I. C.I per Kilo.	A.V. O_2 diff. Vols %.
Average	6.1	91	1.45	4.64 vol. %
Maximum	7.2	115	1.58	4.47
Minimum	4.8	67	1.22	4.83

TABLE 6. 15 Normal Males lying, aged 16 - 46. From the results of Davies & Gilchrist.

Rosen and White[34] while working on the relationship of stroke volume to pulse pressure also made use of the ethyl iodide method. In four normal males of 17-30 years the average circulation rate at rest, lying, was 6.4 L per min., and the average stroke volume 95 cc., while in the same individuals standing the average C.R. was 4.4 L per min. and S.V. 48 cc., a diminution of 31% - 96% respectively.

RADIOLOGICAL METHODS.

Radiography would appear to offer a method of directly observing and measuring changes in the size of the heart, and various observers have thus studied the diastolic size of the heart and the stroke volume.

Meek and Eyster[35] reported in 1923 observations made on a series of 17 normal individuals both at rest and during moderate exercise. By means of an electrical/

electrical device they arranged that photographs could be taken at specific points in the cardiac cycle, as indicated by a string galvanometer, and thus films obtained at the height of diastole and of systole. From the difference in size of the systolic and diastolic shadows the actual output could be calculated by means of a formula. In their series 10 individuals showed an increase in diastolic size and 7 a decrease during muscular exercise. In 11 individuals systolic size was decreased and in 6 increased. The average output per beat during rest was estimated at 79 cc. and during exercise at 94 cc., while the circulation rate averaged 5.9 L at rest and rose to 10.75 litres during exercise. In three individuals there appeared to be a decreased stroke volume during exercise, circulation rate being increased by increase in heart rate alone. In a few experiments there appeared to be an increase in stroke volume during exercise though the diastolic size decreased; an observation which, if correct, would appear incompatible with Starling's theory and "law".

In this connection it is noteworthy that no observer using X-ray methods has reported a marked increase in the diastolic size of the heart during exercise.

CONCLUSIONS.

CIRCULATION DURING REST.

In work on animals the evidence seems in favour of a circulation in the normal resting animal of the magnitude of 1-2 cc. per kilo per beat rather than the smaller circulations, under 1 cc. per kilo., suggested especially by the earlier experiments where the animals were anaesthetized and almost certainly suffering from shock. Yandell Henderson was the first to suggest a resting circulation of such magnitude and his results from anaesthetised animals, have been confirmed by recent work notably that of E.K. Marshall where no anaesthetic was used.

In man at rest the average given in different series of circulation rate estimations varies from 3.68 to 10.11 litres per min. Individual estimations in apparently normal subjects show an even wider variation. This variation can partly be explained by sex. The average of the determination on females in any one series is less than that of the males. This is possibly due merely to the average stature of females being less than of males (since the stroke index does not appear to be less in females). The average size of the subjects may also affect the average circulation rate though it will not necessarily affect/

affect the stroke index. The position in which the determinations have been carried out will certainly affect the average results. It is interesting to note that the lowest averages are those in Krogh and Lindhard's and Burwell and Robinson's series, in which the estimations were done with the subjects sitting. In different series there is no uniformity in the conditions under which resting determinations were made. In some basal conditions were obtained, in others the subjects merely lay down for ten minutes on a couch before the determination. The high average of 10.6 L per min. obtained by Henderson and Haggard in one series is probably partly explained by the short resting period before the determinations. The number of estimations on which the average for each individual in a series was calculated will also have an effect. If one estimation only be done, as in some series, then the average will be high on account of the excitement effect got on all first observations.

These variations in the state of the subject, however, probably do not play so great a part in causing the wide scatter in results as do differences inherent in the various methods. The averages of the various series by the N_2O method are all low. These are the so-called "corrected" results and, as we have seen, it is doubtful if this correction is justifiable. If the actual observed results were

taken and allowance made for the determinations having been made with the subjects sitting, the N_2O results would be of about the same order of magnitude as those obtained by the Fick Method. In some hands the ethyl iodide method appears to have given results ranging rather higher than Fick results.

If series in which the results appear to have been affected by one or other of these factors be omitted, the bulk of the determination of the circulation rate appear to be between 5 and 8 litres per min., and of the stroke volume between 70 and 150 cc. The output per kilo per beat in man at rest, as in experimental animals appears to be between 1 and 2 cc. Davies and Gilchrist, using the same apparatus as the writer, obtained in normal men, lying, results varying between a C.R. of 7.2 L per min. with a S.V. of 115 cc. and S.I. of 1.58 and a C.R. of 4.8 L per min. with a S.V. of 67 cc. and S.I. of 1.22.

Since the circulation rate to be expected in the normal individual at rest has been so indecisively determined, and appears subject to such wide variations, conclusions as to the effect of abnormal states, would appear difficult to make.

CIRCULATION DURING EXERCISE.

Two opposing theories have existed as to the circulatory changes occurring during exercise. In one the oxygen utilization was assumed to remain

constant, the circulation rate increasing in direct proportion to the oxygen consumption by means of increase in heart rate and in stroke volume. In the other the stroke volume was thought to remain constant, any increase in circulation rate being due entirely to increase in pulse rate. The increased amount of oxygen necessary during work was provided partly by increase in circulation rate and partly by increase in oxygen utilization.

Though each of these theories may, in individual cases, provide an explanation of the circulatory mechanism whereby increased metabolism is rendered possible, it is evident that neither can explain all cases. It has now been repeatedly shown that oxygen utilization may and does increase during muscular work, and even Henderson has had to admit that the stroke volume may vary in normal healthy individuals on change of position and during exercise.

The body therefore has three different reserves on which it may call as metabolism increases, increase in pulse rate, increase in the output per beat and increase in oxygen utilization. The extent of these reserves and the relative proportion in which they are used appears to differ in different individuals and possibly in the same individual under different circumstances.

CIRCULATION RATE IN PATHOLOGICAL STATES.

CARDIAC DISEASE.

Valvular Lesions. Meakins and his co-workers (36, 37, 39) using the method elaborated by Meakins and Davies[22] and Mobitz[31] using the ethyl iodide method have investigated the circulation rate in cases exhibiting the commoner valvular lesions.

In "fully compensated" cases of aortic or mitral incompetence they found the circulation rate at rest to be within normal limits. Means and Newburgh[16] who measured the circulation rate during work in a case of aortic incompetence found the changes similar in every way to those occurring in a healthy subject.

Meakins, Dautrebande and Fetter[37] made determinations of the circulation rate on four cases of mitral stenosis, three with normal rhythm, one fibrillating. In each the stenosis was well-marked clinically; and though none of them was fit for much exertion, yet signs of cardiac insufficiency were absent at rest. In three of these cases the C.R. was estimated both at rest and during work; the values which were obtained are averaged in table 7.

TABLE 7./

	P.R.	C.R.	S.V.	Remarks.
1.	100	3.31	33	Rest. Av. of 2 obs.
	1.58	5.0	32	Walking exercise. Severe dyspnoea.
2.	62	2.89	47	Rest. Av. of 4 obs.
	80	3.45	43	Mild exercise. Dyspnoea.
3.	93	3.47	37	Rest. Av. of 2 obs.
	150	4.94	33	Walking exercise. Severe dyspnoea.

TABLE 7. Circulation Rate in Mitral Stenosis. Normal Rhythm (From Meakins, Dautrebande and Fetter.

The results from the case of fibrillation will be considered later. In these cases the C.R. is well below normal limits and the stroke volume is even more markedly diminished, 30 - 50 cc. instead of 70 - 100 cc. as would be expected in normal subjects of the same type.

During exercise, associated in each case with distress out of all proportion to the very moderate amount of work done, there was an increase in circulation rate due entirely to an increase in heart rate, the stroke volume tending to diminish. Mobitz[31] also found that in mitral stenosis the stroke volume was diminished to about 60% of the average value found by him in healthy subjects. Cases of aortic stenosis, congenital heart, and myocarditis are/

are reported by Mobitz to have low C.R.s. with S.Vs. in the same range as in mitral stenosis.

ARRYTHMIAS AND TACHYCARDIAS.

Barcroft[38] while investigating a case of paroxysmal tachycardia found that in ordinary circumstances with the pulse rate varying between 64 and 82 the C.R. in this case was between 5 and 6L per minute, but that during a paroxysm, when the pulse rate would be 175-198, the C.R. fell to 2.5 - 3.86 L per minute.

Meakins and Davies[39] in two cases of Auricular flutter also found that with spontaneous increases in pulse rate there was associated a diminution in C.R.

The case of auricular fibrillation investigated by Meakins and mentioned above provides interesting information.

Date.	P.R.	C.R.	S.V.	Rhythm.
26.5.22	84	3.82	45	Auricular Fibrillation
2.6.22	130	3.68	28	" "
22.6.22	54	5.35	99	Normal Rhythm.
27.6.22	62	4.66	75	" "
7.7.22	72	4.61	64	" "
8.7.22	80	3.95	49	Auricular Fibrillation
28.8.22	67	4.21	63	Normal Rhythm.

TABLE 8. C.R. in a case of Mitral Stenosis during periods of Auricular Fibrillation and of Sinus Rhythm (From Meakins, Dautrebande and Fetter).

Observations were made during periods of fibrillation and of normal rhythm and it was found that with the return to normal rhythm there was on each occasion a definite increase in C.R. resultant entirely on an increased output per beat. A comparison of the first two observations given in table 8 is interesting for, despite an increase in pulse rate from 84 to 130, the C.R. in the second is slightly diminished owing to the very marked decrease in the stroke volume.

Interesting experimental work on the effect of regular and irregular tachycardia on the blood flow in the dog was recently published by Stewart and Crawford.[40] During the actual experiments the dogs were unanaesthetised and unnarcotised; electrodes, by which the requisite type of tachycardia was produced, having been attached under ether anaesthesia on the previous day to the right auricle. The blood flow estimations were done on the Fick principle. During rapid irregular tachycardia such as may occur clinically in cases of auricular fibrillation the C.R. always fell. During rapid regular tachycardia there was in one third of the experiments a decrease in the C.R. while in the others it remained unchanged.

It would appear then that spontaneous tachycardia, or at least tachycardia unassociated with exertion, may, especially if the ventricular rhythm is irregular, be associated with a fall in circulation rate.

CARDIAC FAILURE.

Meakins and Davies[41] report three cases which while under observation developed gross signs of cardiac insufficiency in the resting state (table 9).

Case.	C.R. L per min.	S.V. cc.	H.R.	Remarks.
1	8.0	106	72	No symptoms, at rest.
	2.84	34.5	84	Cardiac Failure. Oedema, orthopnoea etc.
2	7.64	101	76	No symptoms, at rest.
	2.71	30	90	Oedema, orthopnoea etc.
3	6.34	69	94	No symptoms, at rest.
	2.96	30	96	Oedema, orthopnoea etc.

TABLE 9. Low C.R. in Cardiac Failure (from Meakins and Davies).

In each there was a marked fall in circulation rate due entirely to diminution in the output per beat. The rhythm in each of these cases was normal, two had aortic incompetence, the last had no valvular lesion.

Previously Lundsgaard[42] and separately Harrop[43] had indicated that in cardiac failure the C.R. was probably low. They found a definite increase in the oxygen utilization of blood passing through the arms of patients showing signs of cardiac insufficiency. In "fully compensated" cases with valvular and other cardiac/

cardiac lesions they found the peripheral oxygen utilization to be normal.

ANAEMIA.

Investigation into the circulatory changes resultant on anaemia have been carried through by various workers. The earliest in this field were Krause[44] (1897) and Plesch[44] (1909) who both observed an increase in the cardiac output in severe anaemia.

More recently Harrop[43] in three cases of severe anaemia found a marked decrease in the oxygen utilization of the blood passing through an arm, indicating an increased rate of blood flow through the limb. In a similar but more exhaustive investigation Lundsgaard[45] found no change in the oxygen utilization so long as the haemoglobin was above 30%. With the Hb. under 30%, i.e. with the oxygen content of the arterial blood less than the usual Art. Ven. oxygen difference, there was a marked and progressive increase in the rate of flow. From his results Lundsgaard concluded that "the resting anaemic organism does not increase its circulation until all the reserve oxygen is used".

Dautrebande[46] using the method of estimating the C.R. associated with the names of Meakins and Davies, found in four anaemic patients, (three pernicious anaemias and one chlorosis) observed over long periods, /

periods, no change in the cardiac output with the Hb. over 50%, a moderate increase when the Hb. was between 40 and 50% and a marked and progressive increase when the Hb. fell below 40%. Liljestrand and Stenstrom[47] also noted an increase in C.R. in four cases of anaemia which they examined by the nitrous oxide method of Krogh and Lindhard. This increase they found was due to an increased output per beat rather than an increased pulse rate.

Recently experimental work was done on this subject by Blalock and Harrison[48] working with unanaesthetised dogs, the C.R. being estimated by the Fick method. They found that a diminution in the Hb. content of a dog's blood, such as may be produced by repeated small haemorrhages, is associated with an increased cardiac output. This increase in the circulation rate was noted to reach a maximum during the period of recovery, i.e. after the bleedings had been stopped.

Meakins and Davies[49] while emphasising that theoretically an increase in C.R. is to be expected in anaemia, state that in two cases examined by them the circulation rate was not specially high. Similarly Mobitz[31] found that in those cases of anaemia whose C.R. he estimated by the ethyl iodide method, the stroke volume was either normal or very slightly increased. He does not mention pulse rate or/

or circulation rate, presumably these also show little departure from normal.

Notwithstanding those results last quoted it would appear probable from the others that, in severe anaemia at least, the circulation rate is usually increased.

HYPERTHYROIDISM.

Meakins, Davies and Sands[50] investigated the C.R.s of 14 cases of hyperthyroidism and of one case of myxoedema on thyroid extract. In the hyperthyroid cases the C.R. was generally found to be high at first and, as the symptoms subsided under treatment, to decrease to an approximately normal level. Although the changes in C.R. and metabolism were in the same direction, no complete parallelism could be traced between the two in the individual cases. In this series the increase in C.R. appeared due to an increase in both pulse rate and stroke volume; and in several cases after operative treatment there was a fall, not only in metabolism, pulse rate and circulation rate, but also in the output per beat. The myxoedema while she was under observation was on large doses of thyroid extract, and her metabolism throughout was above normal level, so that no information as to the C.R. at low metabolic rates was obtained.

Liljestrand and Stenstrom[51] compared by the nitrous /

nitrous oxide method the circulation rates in a group consisting of 7 males and 3 females, all healthy, and a group of 8 females and 3 males suffering from exophthalmic goitre. A notable increase in the C.R. was found in the cases of exophthalmic goitre, amounting on an average to 80% in the females and 100% in the males. This increase in C.R. was due entirely to increase in pulse rate, the stroke volumes in the exophthalmic cases being in this series no larger than in the normals. The oxygen utilization was, on account of the high C.R., lower in some of the exophthalmics than in the healthy patients.

These results obtained in man have been paralleled by results obtained by Blalock and Harrison[48] in dogs, for on feeding thyroid extract to healthy dogs they found that a definite increase in the rate of blood flow occurred.

OTHER CONDITIONS.

The circulation rate in some other conditions has been investigated by Mobitz[31]. Thus in cachectic people and patients long bedridden he found the C.R. and S.V. to be low. In acute febrile conditions, e.g. malaria, the C.R. rate was increased during the febrile period, the increase being entirely due to the increased pulse rate; while in long continued fever the C.R. was either normal or slightly below normal./

normal. In fat people the stroke index (stroke volume per kilo per beat) was less than that found in the normal controls.

THE EFFECT OF DIGITALIS ON THE CIRCULATION RATE.

The only actual measurements of the effect of digitalis on the circulation rate in man which have been published appear to be those of Eppinger, Von Papp and Scharz[52]. Using a modification of the Plesch method they observed the effect of digitalising two cardiac patients. In one there was a diminution in the C.R. definitely related to the digitalis; in the other there was also a diminution, but this could not wholly be attributed to the drug.

Cohn and Stewart[53] studied the effect of digitalis on the size of the human heart by means of the moving orthodiagraph, and noticed in each case examined, a definite increase in the ventricular excursion after digitalis, suggestive of an increased output.

Other workers (Vagt; Kaufmann)[54] have described a slight increase in the output per beat, associated with a fall in the general circulation rate. Their methods however were so extremely indirect and the calculations so involved as to render the results of little value.

Numerous efforts have been made to answer the question as to whether digitalis increased or diminished the circulation rate by experimental work on animals. The literature on this has recently been reviewed by Cushny[55] and seems to indicate that while the/

the output per beat is usually increased from a direct action of the digitalis on the cardiac muscle, and that this usually results in an increased output per minute; yet if very marked slowing or irregular cardiac action occurs, this may be sufficient to outbalance the increase in S.V. and to diminish the C.R. From a consideration of these experiments he states[56] "it may be taken that, in therapeutic doses, digitalis increases the amount of blood expelled by the heart per unit of time and thus augments its efficiency".

Since Cushny's review was published, Henderson and Blalock[57] working with healthy unanaesthetized dogs and ordinary therapeutic doses of digitalis found in every instance a diminution in C.R. after digitalis. The amount of the decrease varied in different animals, but was on an average 25%. It reached its maximum 6 hours after the digitalis was given (intramuscularly), remained at maximum for 48 hours, and then the C.R. gradually increased, the original level being reached after 6-7 days. In a dog with auricular fibrillation a similar result was observed. Although the decrease in C.R. occurred in all the experiments, the changes in heart rate, stroke volume and oxygen utilization varied. In some cases there was an increase in heart rate, the decrease in the C.R. then being due to a diminished output per beat.

The/

The effect of digitalis on the circulation rate still appears to be doubtful, and information as to the change in cardiac output produced by it in man, and especially in cases of cardiac failure, is almost entirely lacking.

THE ETHYL IODIDE METHOD.

The circulation rate as determined by the ethyl iodide method, the principle of which has already been outlined, is calculated according to the equation.

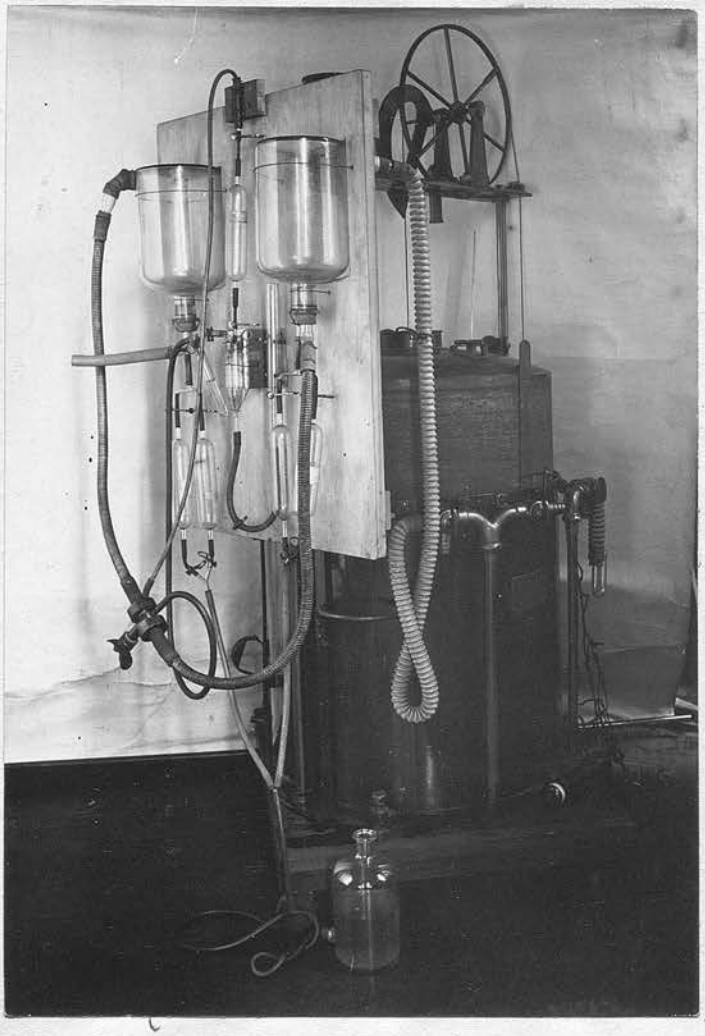
$$C.R. = \frac{(E.I.\text{ in insp.air} - E.I.\text{in exp.air}) \times \text{min.resp.vol.}}{E.I.\text{ in alv. air} \times 2.}$$

Or, more simply the circulation rate equals the amount of ethyl iodide absorbed per minute divided by the amount carried away in each litre of blood passing through the lungs. The correctness of this equation depends on two factors, viz. (1) that in the concentration and amount used none, or only a negligible quantity, of the ethyl iodide absorbed returns in the venous blood, and (2) that the coefficient of solubility of ethyl iodide in blood is 2. Henderson and Haggard[1] satisfied themselves that these two factors were correct, and were also satisfied that an accurate analysis of ethyl iodide either in air or in solution could be made with the iodine pentoxide train.
Of the other workers who have used the method, while most have suggested minor alterations in technique and apparatus, none have questioned these fundamental factors except Starr and Gamble[58] in a very recent paper.

Doubting the reliability of the iodine pentoxide method/

method for the analysis for ethyl iodide, which they considered was subject to variation by factors over which the analyst had no control, they worked out another method of doing the analysis dependent on the reaction of ethyl iodide with silver nitrate. This method they considered accurate to within 2-3% and subject to no unknown factor of error. Using their own method they worked out the coefficient of solubility of ethyl iodide in blood and found it to be 7.6. They also found that ethyl iodide was destroyed but slowly while in solution in blood in vitro, and that expired air collected in a spirometer might contain a considerable quantity of ethyl iodide. They therefore consider that the ethyl iodide method is fundamentally wrong; and are of the opinion that it gives results consistent with those obtained by other methods only because the inherent errors tend to cancel each other. These results and conclusions depend entirely on the accuracy of the new method of analysis used, and this is at least as much suspect as that of the iodine pentoxide method.

As yet no other workers have published evidence supporting the conclusions of Starr and Gamble, nor on the other hand have their conclusions or their analytical method been definitely shown to be wrong. However, if the method was so entirely fallacious, it seems improbable, in spite of the explanation given, /



given, that results so closely resembling those from other methods and so consistent in series on single individuals should have been obtained by it. It is hoped that the results given below will be sufficiently consistent to demonstrate that the method cannot be wholly inaccurate.

APPARATUS.

The apparatus, of which a photograph is given, used in these circulation rate determinations, was that with which Davies and Gilchrist did the series of observations on normal subjects mentioned above, and differs in a few details from the apparatus originally described by Henderson and Haggard. It consists of a spirometer of 200 litres capacity, accurately counterpoised, the scale being marked off in litres. To the spirometer inlet is fixed a glass U tube in which the requisite amount of ethyl iodide can be placed so that air drawn into the spirometer vaporises the ethyl iodide and charges the spirometer with the correct concentration of vapour. A rotary fan in the interior of the spirometer driven by an electric motor outside, keeps the contents properly mixed. As ethyl iodide would react with exposed metal the inside of the spirometer and of all metal parts is coated with red lead. The outlet is fitted with a three-way stopcock so that the patient may breathe from the spirometer or from the outside air, the spirometer then being shut off. From the outlet /

outlet a length of 1" bore corrugated rubber tubing leads to an inverted 5 litre glass bottle or mixing chamber. The cork in the underlying neck of this bottle is pierced by a 1" bore glass tube which connects with a flexible metal tube of similar bore leading to the inspiratory valve. A narrow bore glass tube also passes through this cork and bifurcates outside.

To this are attached two 250 cc. sampling tubes for obtaining samples of inspired air. A similar inverted 5 litre glass bottle connected in a like manner serves as a mixing chamber for the expired air. Through the neck of this bottle there is an outlet to the exterior, and as before a bifurcated glass tube from which the expiratory sampling tubes are suspended. This tube has a side arm from which samples of expired air can be obtained for analysis for CO_2 and O_2 in the Haldane apparatus. The lower ends of the four 250 cc. sampling tubes are attached by rubber tubes to a moveable reservoir. At the beginning of an experiment they are filled with water from this reservoir and samples from the mixing chambers are obtained by allowing this water to drain off.
The gas sampling tubes are of glass, 250 cc. in capacity, with at each end a piece of rubber tubing closed by a spring clip. Glass stop-cocks cannot be used since the ethyl iodide is absorbed in appreciable/

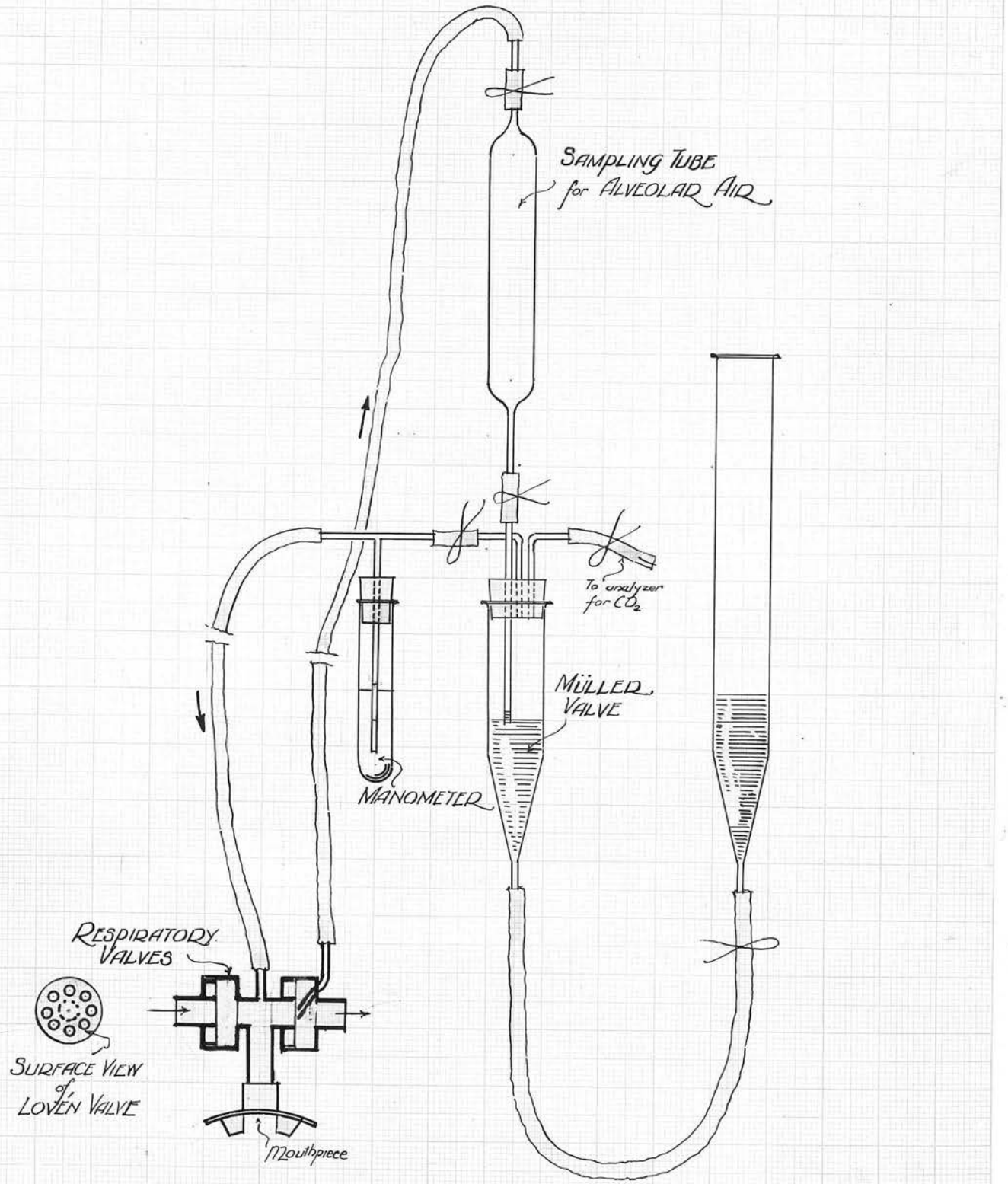

Sampling Tube
for Alveolar Air
To analyzer
for CO_2
Müller
Valve
Manometer
Respiratory
Valves
Surface View
of
Loven Valve
Mouthpiece

Diagram 1

appreciable amount by the grease required for the cocks.

The apparatus used in obtaining the alveolar sample is shown in diagram I. It consists of a mouthpiece attached to a metal chamber containing inspiratory and expiratory valves, those used being of the Lovén type. There are two small extra outlet tubes, one from the space between the valve and the other from just beyond the expiratory valve. This latter is connected by a piece of flexible metal tubing to a gas sampling tube. The outlet between the valves is connected by a rubber tube to a Müller valve below the sampling tube. On this piece of tubing there is a screw clip and a simple water manometer is interpolated here.

The circuit thus formed is such that a small portion of the air just beyond the expiratory valve is drawn back at the beginning of each inspiration into the sampling tube by the slight negative pressure then existing in the chamber between the two valves. By this means a sample of air from the end of each expiration is automatically drawn into the small circuit which soon becomes filled with air corresponding closely with that in the lung alveoli. The size of each sample thus withdrawn should be between 10 and 20 cc. and this can be judged by the amount/

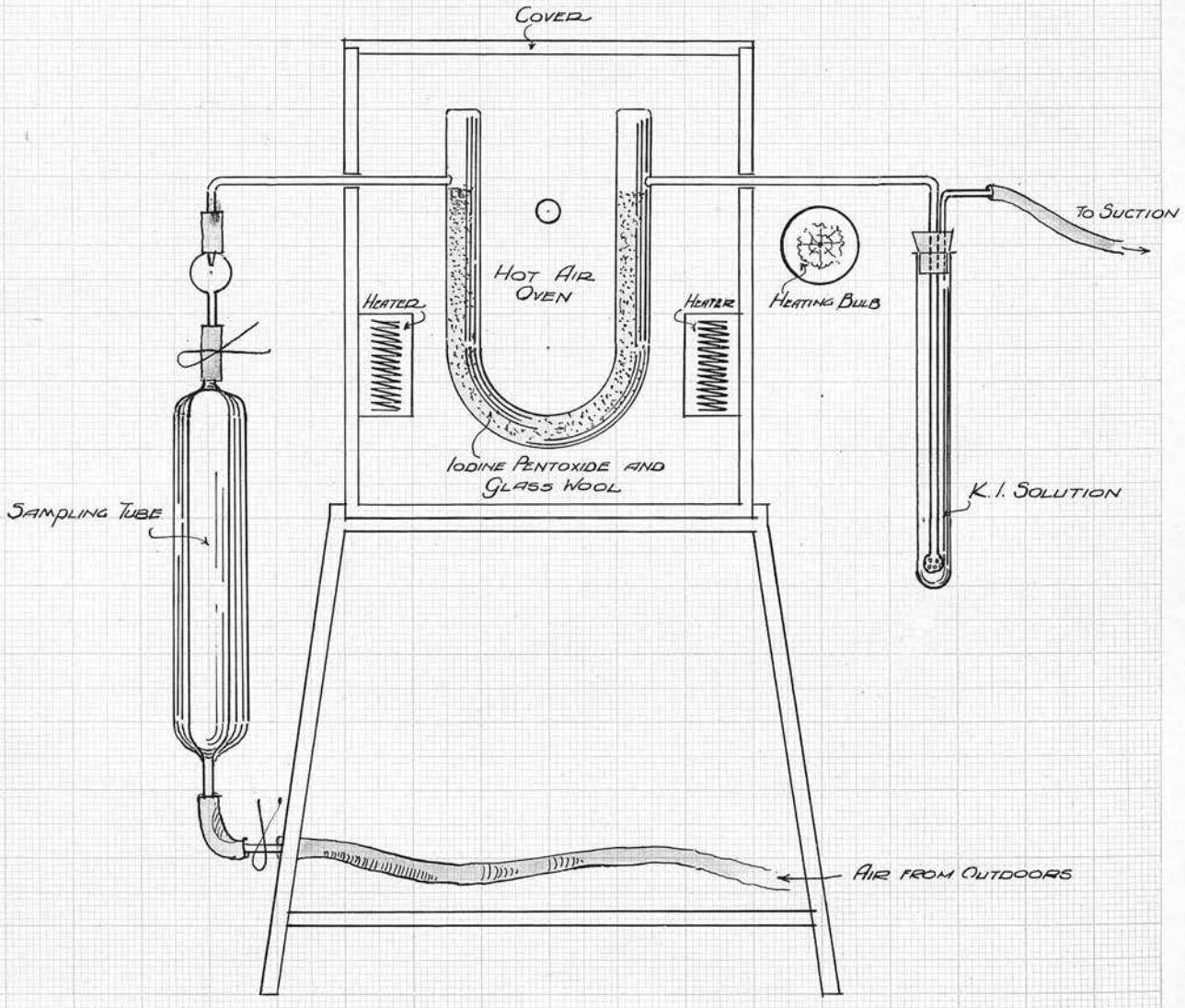

Cover
Hot Air Oven
Heater
Heater
Heating Bulb
To Suction
Iodine Pentoxide and Glass Wool
K. I. Solution
Sampling Tube
Air from Outdoors

Diagram 2

amount of air bubbling through the Müller valve. Alterations in the size of the samples can be made by varying the lumen of the corrugated rubber inspiratory tube with a screw clip and so varying the strength of the inspiratory pull. This automatic method has been tried out against the Haldane Priestley method by Henderson,[59] Cullis, Randel and Dahl,[32] and Davies[63] and these workers have found that a true alveolar sample can be obtained by it. As will be seen below, the CO_2 content of the alveolar samples obtained, especially in the cardiac cases, tends to be low, possibly lower than one could reasonably expect in such cases.

APPARATUS USED FOR ESTIMATION OF ETHYL IODIDE.

To estimate the concentration of ethyl iodide in an air sample the contents of the sampling tube are sucked through a U tube heated to 200°C., and containing a mixture of iodine pentoxide and glass wool. Iodine is liberated according to the equation

$$10\ C_2H_5\ I + 13\ I_2O_5 = 20\ CO_2 + 25\ H_2O + 36\ I.$$

and is collected in potassium iodide solution. The amount of iodine is estimated by titration with a dilute thiosulphate solution, using starch paste as an indicator.

The apparatus used is shown in diagram II. An electrically heated hot air oven was employed.

This /

This is safer than the hot oil bath originally suggested by Henderson and Haggard, but a uniform heating of the pentoxide tubes is more difficult to attain especially if four are used.

Each U tube contains 40-50 G of iodine pentoxide intimately mixed with glass wool and firmly packed. At the end of the side-arm for the sampling tube there is a simple trap to prevent an undue amount of moisture reaching the pentoxide. The other side tube passes through a rubber cork into a boiling tube containing 2% pot. iodide solution and ends in a perforated bulb. For suction a filter pump with a strong head of water was used, and this was found satisfactory even when four pentoxide tubes were in use.

The inlet tube communicates with the outside air, since carbon monoxide, and other gases which decompose iodine pentoxide, may be present in sufficient concentration in room air to cause a considerable liberation of iodine.

Before it is used for analytical purposes it is necessary to condition the pentoxide. This is done by keeping the oven at a temperature of 250°C. for 24 hours while a steady stream of air is drawn through the tubes; a large amount of iodine is given off during this conditioning process. When properly

conditioned/

conditioned a certain amount of spontaneous decomposition of the pentoxide still goes on at the analytical temperature (200°C.) The amount of iodine thus being given off can be determined by a blank run before commencing an analysis and, with properly conditioned tubes, should be negligible.

A very dilute thiosulphate solution is used for the titration. The actual strength is unimportant so long as it is kept constant, since the amount of thiosulphate used to titrate the iodine liberated from each sample is applied without conversion into the corresponding amount of ethyl iodide, to calculate the rate of the circulation.

TECHNIQUE.

Preparation of Patients.

As the spirometer with its attachments was too large and cumbrous to be moved about a ward it was kept in a corner of the convalescent room. Patients whose circulation rate was to be estimated were wheeled out of the ward in their beds into the convalescent room. This was an easy matter, special wheeled beds being available. Patients from other wards were brought along lying on trolleys. In the case of out-patients and convalescent patients who were up and about, the estimation was done with the subject/

subject lying on a couch. These patients rested thirty minutes on the couch before an estimation was made. The greater number of estimations were made between 9 and 11 a.m. - 2-4 hours after the patient's breakfast. It was not found feasible to do the estimations with the patients fasting, except in the exophthalmic goitres and myxoedemas, which cases were done immediately after the routine B.M.R. estimation. Thus by having the patients at rest, in a lying position, and as far as possible in the same state as regards food, an endeavour has been made to secure uniform conditions throughout the series of cases. In dyspnoeic cardiac patients a completely recumbent position was usually not possible, and these cases were kept in the more comfortable propped up position, the same position being maintained from day to day.

Collection of Samples.

The spirometer having been charged, the sampling tubes attached, and the level of the water in the Müller valve adjusted, the mouthpiece is placed in the patient's mouth and nasal breathing stopped by applying a nose clip. For the comfort of the patient it was found advisable to devise a means of suspending the mouthpiece and so taking the weight off the patient's gums. The amount of air bubbling through the Müller valve with each inspiration is now adjusted to/

to between 10 and 20 cc. by tightening or loosening the screw clamp on the inspiratory tubing. A few minutes are allowed for the patient to become accustomed to breathing through the valves, and for the pulse to reach a basal level, and then by turning the stopcock the patient is connected with the spirometer and the period started. A ten minute period is employed, the timing being done with a stop watch. During the first five minutes counts of heart rate and respirations are made. At 6 minutes a sample of expired air for CO_2 and O_2 analysis is taken in a Haldane vacuum tube, and thereafter the water drained off from first the inspiratory and then the expiratory sampling tubes and these samples secured. At 9½ minutes the small circuit is closed off and the alveolar sampling tube clipped. At 10 mins. the spirometer is shut off and the reading taken. The patient is now relieved of mouthpiece and nose clip and a sample from the Müller valve taken for analysis for CO_2. The reading of the thermometer in the spirometer is noted.

Patients soon get accustomed to the apparatus and for the most part breathe easily and naturally. Occasionally with dyspnoeic cardiac patients it was found advisable to shorten the period to 7 or 8 minutes. One patient at least, found the procedure so much to his liking that he was able to fall asleep during

a/

a determination.

With the nose clip in position most are unable to detect the ethyl iodide when they commence to breathe from the spirometer, but at the end of the period when the nose clip is taken off, the odour of the gas is usually noticed. The amount of iodine absorbed at each experiment corresponds to .2 - .5 G of sodium iodide; no symptoms of iodism were noted in any of the cases.

Analysis of Samples.

For each estimation there are seven samples to analyse, five for ethyl iodide, a sample of expired air for CO_2 and O_2, and a sample of alveolar air for CO_2. To expedite matters the oven, early on, was altered to contain four pentoxide tubes instead of two as originally.

While the samples are being collected the oven is heating up to 200°C., and, before the actual analysis is commenced, a blank run should be instituted, to ensure that the spontaneous decomposition of the pentoxide in each tube is minimal. In the actual analysis a period of 15 minutes is employed; during the first six minutes the rate of flow is kept slow, thereafter the full force of the suction is used. A fifteen minute period was found desirable since with a period of less duration and the rate of suction available, all the iodine from the higher concentra-

tion/

concentration inspiratory samples was occasionally not obtained. A blank run of 5 minutes is carried out between each analytical period to ensure that all the iodine has been carried over. During this five minutes blank run the contents of the absorbing tubes are titrated, the fifteen minute periods being thus left free for the air analyses. The analysis of a complete set of seven samples takes at least one hour. Three determinations were usually done in a day, 1-1½ hours being necessary for the collection of the samples in the mornings and 3 hours for the analyses in the afternoon.

Calculation of Results.

As previously explained the amount of thiosulphate solution used to titrate the iodine liberated from each sample is applied directly to the calculations of the results, which as a consequence is much simplified. Since the sampling tubes vary in their actual capacities, the figure resulting from each titration must be corrected to 250 cc., the capacity of a standard tube. The figures for the two inspiratory and the two expiratory samples are thus averaged and the differences obtained. The respiratory volume, from the spirometer readings, is corrected to normal temperature and pressure by application/

application of the appropriate factor. The product of these two divided by double the alveolar figure (coefficient of absorption = 2) gives the circulation rate. The stroke volume is the C.R. divided by the average heart rate while the stroke index is the S.V. $\div$ the weight of the subject in kilos.

From the CO_2 and O_2 content of the expired air and the minute respiratory volume the amount of oxygen absorbed per minute is calculated. This figure divided by the C.R. gives the difference in O_2 content per litre of the arterial and mixed venous blood; the Art. Ven. O_2 difference has been converted into volumes per cent in the tables given.

OBSERVATIONS.

In all 215 circulation rate determinations have been made on 26 patients suffering from various diseases. These observations have been divided into four groups, those from patients with (1) cardiac lesions, (2) anaemia, (3) metabolic disturbances, and (4) those from a small group showing lesions not falling under any of the above heads. In each of the four sections thus created, short clinical histories of the cases are given, the results tabulated and special points rising in the individual cases discussed. Thereafter the conclusions to be drawn from the results in that section are discussed.

CARDIAC LESIONS.

The first three cases each showed, at some period while they were under observation, definite signs of cardiac insufficiency in the resting state, and each responded to the therapeutic measures adopted. As these cases were all under observation for a considerable period, fairly complete records of the circulatory changes associated with their clinical improvement and with the therapeutic measures adopted have been obtained.

When the failure was clinically most manifest, at/

at the commencement of the period of observation in the first two, and on readmission in the third, the circulation rate was at its lowest, and with improvement in the clinical condition of these patients there was in each case a definite increase in the C.R. During the period of marked failure the heart rate was rapid, the low C.R. being due apparently to the very small output per beat.

In Mrs S. and J.H., both fibrillators, the S.V.s have been calculated directly from the heart rate, and since there was in each case a large pulse deficit, the value for the S.V. obtained thus is much less than if the pulse rate had been used. In both the pulse countable in the radial artery during the period in question was about 100 per minute, and the values for the S.V. using this figure are 36 and 30.5 cc. in place of 18 and 21 cc. With the ventricular output varying from beat to beat as, from comparison of pulse and heart rate, it manifestly does in these cases, the average S.V. may be expressed as the mean output of the actual number of contractions, or as the mean output of those contractions sufficiently strong to produce a pulse at the wrist, assuming then that all the other contractions are totally inefficient. Which of these approximations would be most useful is doubtful. In these tables the S.V. has been calculated from the actual heart rate in every case whatever/

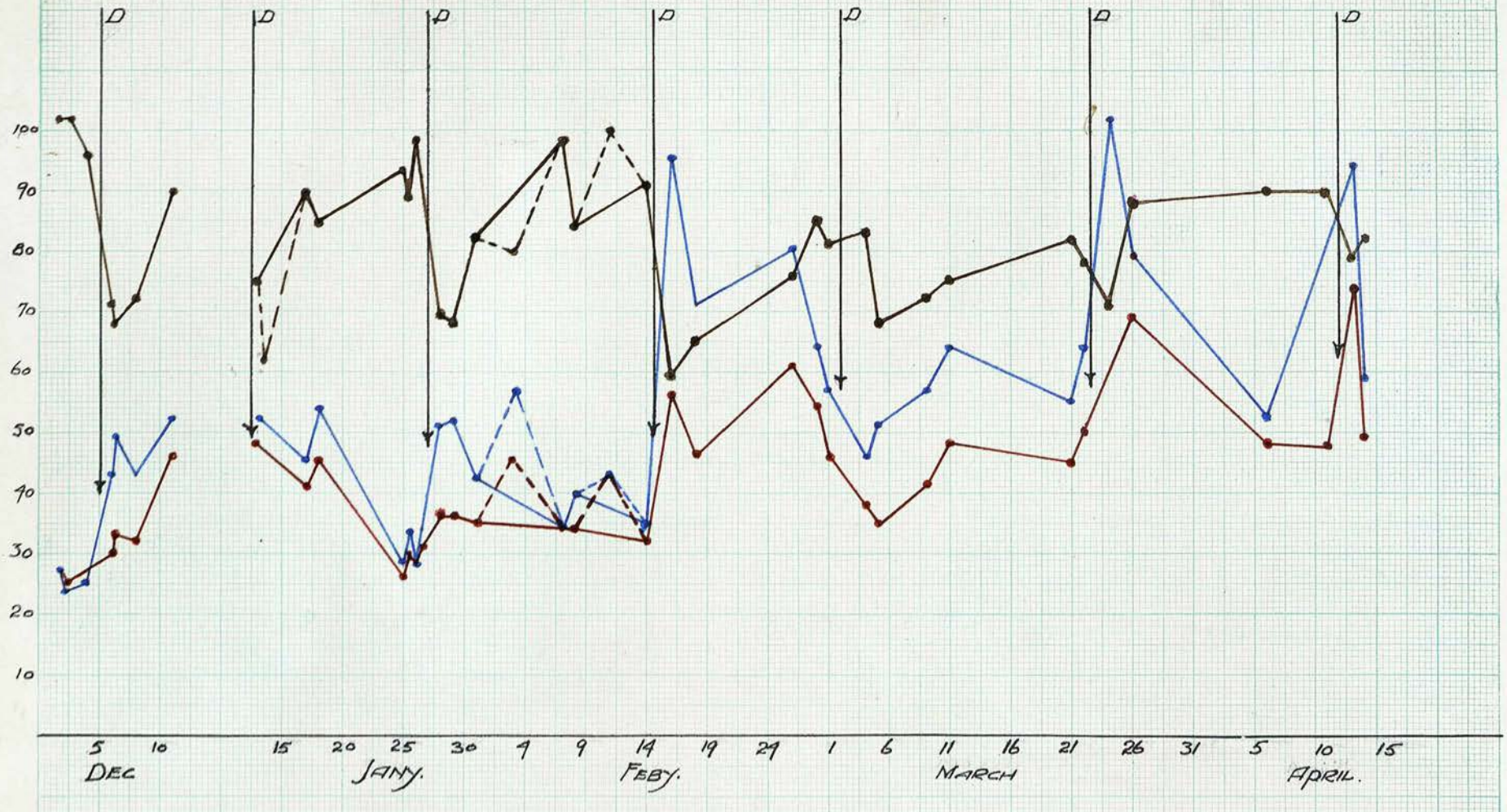


CHART. 1. Mrs. D.

Circulation Rate
Stroke Volume
Heart Rate

whatever the rhythm.

The stroke index in these three cases is, on account of the small S.V., extremely low especially in J.H., a heavy woman. The changes in the oxygen utilization are in the opposite direction to those in the C.R., being high when insufficiency was most marked, and decreasing as the C.R. increased and the patient's condition improved.

In order that the changes in the circulation of these three patients while they were under observation might be more easily studied, the results have been charted out as well as being given in the tables. (Chart 1 - see opposite).

On Chart 1 are the results from Mrs D. on whom 40 observations, covering a period of 4½ months, were made. Heart rate, circulation rate and stroke volume appear on this chart, oxygen utilization having been omitted to avoid undue complication. Taking first the C.R. it is seen to rise very definitely during the period of observation, commencing at 2.5 - 2.7 litres and during the last months not falling below 4 litres. This rise in level is not uniform for after each dose of digitalis (D) there is a more or less marked increase in C.R. which gradually falls off to be increased again, before the former level is reached, by a further dose of digitalis. An irregular staircase/

staircase effect is thus produced. Superimposed on this and to some extent obscuring it are observations, chiefly individual, for whose variation from the common trend some cause other than digitalis must be sought.

The stroke volume follows roughly the C.R., the increase resultant on digitalis being however much more marked on account of the associated pulse slowing. The changes in heart rate are the reverse of those in the C.R., there being a slight lowering of the level over the whole period with more or less marked slowing after each dose of digitalis. The line indicating H.R. is more irregular than the line indicating C.R.

Those aberrant determinations mentioned above require further investigation. They may be due to experimental error, but no evidence of this, though carefully searched for, has been found, and these observations cannot be discarded. Either then undetectable sources of error, as suggested by Starr and Gamble (pp. 55) do exist in the method or these determinations indicate real changes in the C.R. That the latter assumption is correct appears possible for in most instances factors which would explain a change in C.R. can be put forward. In the first of these determinations, done on 11.12.26, the C.R. appeared to be 4.6 L. having been three days previously 3.2 L. This increase of 44% in the C.R. was/

was associated with an increase of 26% in H.R. and 21% in S.V. Excitement or previous exertion might conceivably have produced such an effect but there was no evidence of either. On examining the ward charts, however, there was on this day a rise from the previous day of 1°F. in the temperature level, 10 in the pulse and 8 in respirations. Possibly the rise in C.R. was due to the same cause as this rise in temperature, mayhap some easily overcome infection.

Next on 13.1.27 the C.R. when estimated in the morning was 4.8 litres and in the afternoon 3.2. This 33% decrease was associated with a fall of 17% in H.R. and 17% in S.V. These estimations were done the day after a massive dose of digitalis which had produced much nausea and vomiting. Two hours before the first determination the patient had been vomiting and during the second he had a marked feeling of nausea. The very slow pulse rate at the second determination is possibly then partly due to increased vagal tone resultant on the nausea and the slowing in C.R. is of course to a large extent due to the slowing of the heart rate. Whether the diminution in S.V. may similarly be the result of nausea or whether the C.R. and S.V. in the morning were high as a result of the muscular exertion involved in vomiting or because the determination is the first after readmission, is not clear. It cannot be assumed that increased vagal tone/

tone diminishes the S.V. as well as the heart rate.

On the 3rd of February the patient during the determination was for some reason restless and ill at ease, and the result is an increase of 31% in C.R. and 36% in S.V. without however any significant change in heart rate. On the 11th February the patient's pillows were removed during the determination (for comfort she usually had five). This did not cause breathlessness but the change in procedure alarmed and excited the patient, and, as compared with the previous estimation, there is on this day an increase in C.R. of 26%, in H.R. of 19% and in S.V. of 7%. This increase in C.R. from the associated increase in heart rate (cf. table 2, pp.26), is probably due to the excitement rather than to the change in position. Restlessness and excitement while both increasing the C.R. appear here to have done so in different ways, the former by an increase in S.V., the latter chiefly by an increase in heart rate.

Between 28.2.27 and 11.3.27 there is a portion of the chart differing from the remainder. At the commencement of this period the C.R., which after the dose of digitalis on 14.2.27 had been very markedly raised, began to fall gradually and continues to fall until the 5th of March, and this notwithstanding a full dose of digitalis on the 2nd. The next determination on the 9th shows a rise, and this continues in the succeeding/

succeeding estimations up to the 22nd when a further dose of digitalis producing the usual increase in C.R. was given. Why this dose of digitalis alone of those given to this patient should produce no apparent effect on the C.R. is not clear. On examining the ward chart there is no lowering of the pulse level which can be associated with this dose, though the heart rate as determined at the estimations would suggest a delayed fall. There was however no doubt that this dose was absorbed, for it was followed by very severe nausea and vomiting of the true toxic type, and in a series of electrocardiograms a distinct prolongation of the P.R. interval was noted after it.

On the 13th April a new expiratory valve proved noisy and disturbed the patient, and as a result it is very doubtful whether the increase in C.R. noted can be attributed to the immediately preceding dose of digitalis, especially as the determination on the next day shewed the C.R. back almost to the level obtaining before the digitalis was given.

The effect of the doses of digitalis given to this patient, with the exception of those above mentioned, was to increase the C.R., this increase being due entirely to increase in the S.V. The general increase in C.R. observed is also due to increase in S.V. and parallels more or less accurately the improvement of the patient from a state of complete cardiac/

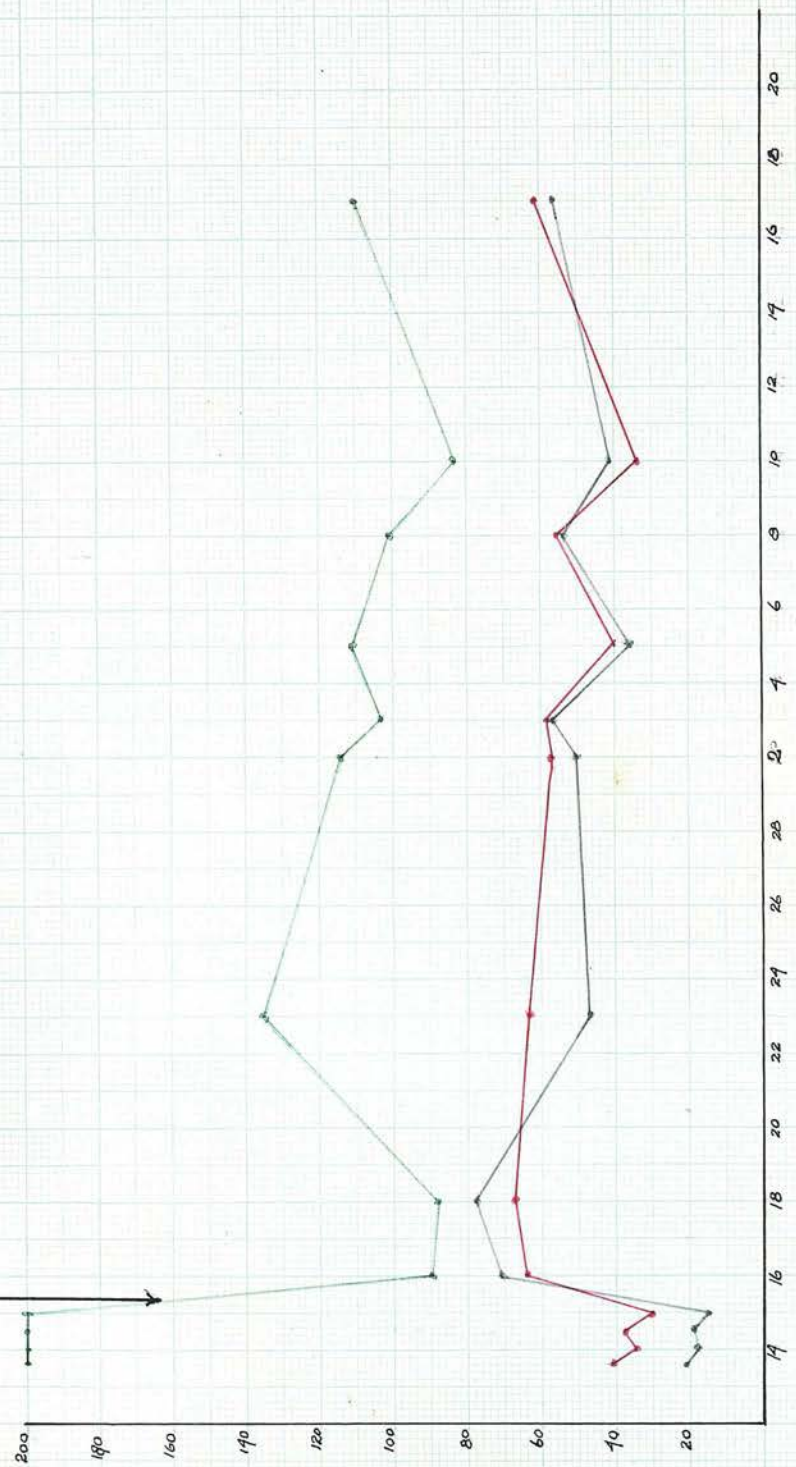


CHART. 2 MRS. S.

CIRCULATION RATE
STROKE VOLUME
HEART RATE

cardiac insufficiency to one in which sufficient reserve force had been gathered to enable her to walk about quietly.

With the increase in C.R. there is a corresponding though, on account of the fairly wide variations occurring in the oxygen consumption, not quite proportional decrease in oxygen utilization. Thus the oxygen utilization shows a marked diminution after each dose of digitalis which produces an increase in C.R. and is at the end of the series on a much lower level than at the commencement.

In this series the values obtained for the CO_2 content of the alveolar air are extremely low, especially early on. With orthopnoea one would expect a low alveolar CO_2, but probably this has been exaggerated here. The alveolar CO_2 is definitely higher towards the end of the series than at the beginning, and in some instances there is a rise following digitalisation. The minute respiratory volume is throughout this series high, especially so at the beginning. There appears to be a tendency for the respiratory volume to fall after digitalis.

In Chart II are the figures from Mrs S. on whom 13 determinations were made over a period of one month. A case of Auricular fibrillation dependent probably on a myocarditis with no apparent valvular lesion, the patient had on admission a ventricular rate uncountable/

uncountable accurately by ordinary clinical methods, but which in an electrocardiogram was seen to be 200 per min. The pulse rate, as nearly as it could be counted, ranged at about 100 per min. With this extremely fast ventricular rate the C.R. averaged 3.6 L. per minute, fully one litre faster than in Mrs D. when first observed. This difference is to some extent upheld by the difference in the clinical condition of the two patients for Mrs S., though having the extremely rapid heart rate and a marked venous pulsation in the neck, had no oedema and showed no breathlessness when supported by three or four pillows. She also improved much more rapidly than did Mrs D.

The effect of the first dose of digitalis here is very dramatic, - an immediate increase in C.R. to 6.4 L. and, since the ventricular rate fell from 200 to 90 wiping out the pulse deficit, a very marked increase in S.V. from an average of 18 cc. up to 71 cc. Even though the S.V. is calculated from the pulse rate the increase is still marked - 36-71 cc. The C.R. is maintained above 5.5 L. until 8.3.27 apart from one determination on the 5th March, made with the patient feeling out of sorts and breathless, when it was 4 litres per minute. The dose of digitalis on the 9th March is followed by a fall in H.R., C.R. and S.V., again possibly partly due to nausea. A week later heart rate, C.R. and S.V. are again back

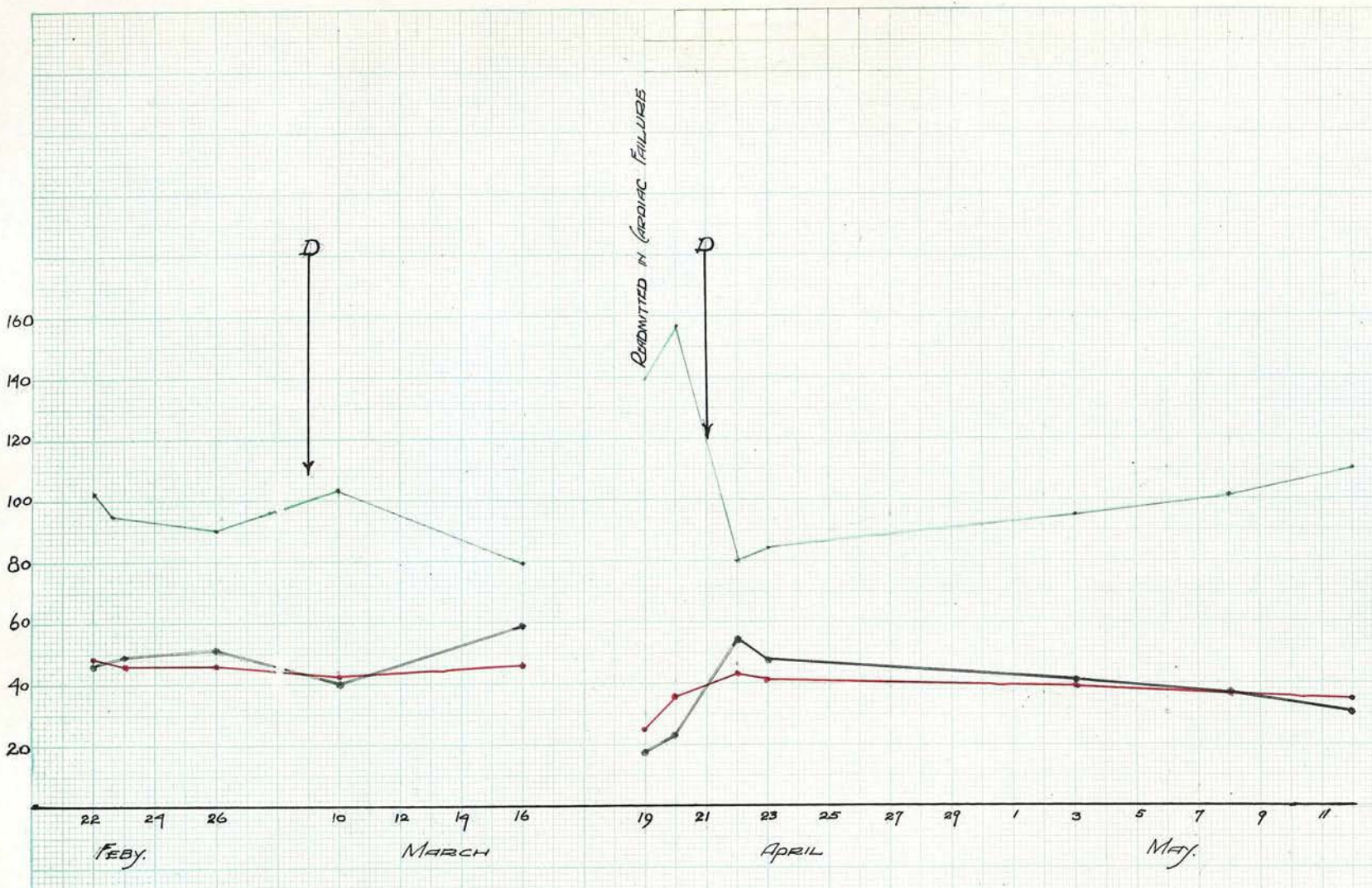


Chart 3 J.H.

Circulation Rate
Stroke Volume
Heart Rate

each to about the old level. An insufficient number of determinations have been made after this dose to be certain of its effect.

Associated with the increase in C.R. occurring here there is, as in Mrs D., a diminution in oxygen utilization. The alveolar CO_2 content is never so low as in Mrs D. but shows the same tendency to increase in later observations. There is no increase in the alveolar CO_2 content after digitalisation in this case, though a definite fall in the minute respiration volume occurred after the first dose of digitalis.

In the case of J.H. (Chart III) 12 determinations in two series were made in a period of $2\frac{1}{2}$ months. During the first series the patient though fibrillating showed no signs of cardiac insufficiency while at rest and her C.R. remained at a level between 4.2 and 4.8 litres. A dose of digitalis did not appreciably affect it. The S.V. varied between 59 and 40 and the oxygen utilisation between 5 and 6 vol %. After the termination of this first series the patient was discharged to a convalescent home from which she was readmitted on the 18th April extremely orthopneic and slightly cyanosed, with a ventricular rate of 140-160 and a pulse deficit of about 50. Her C.R. and S.V. were now definitely diminished, the average for the two determinations made being 3.05 litres and 20.5 cc.

On/

On the exhibition of digitalis these functions returned to approximately the levels they had maintained in the first series. On this occasion, however, these levels were not maintained, a gradual return towards failure values occurring during the three weeks further in which this patient was kept under observation.

The next case, J.D., also exhibited well marked signs of cardiac failure, but unlike the first three cases did not improve with treatment and eventually two months after the period observed, died. Seven determinations of the C.R. were made over a period of 12 days and during this time the C.R. remained between 2.1 and 3 litres per minute, a full dose of digitalis having no effect on the C.R. or, from the ward chart, on the pulse rate. The pulse rate during the circulatory experiments before digitalis was definitely higher than during those experiments done after it, but this is probably due to an excitement effect in the earlier experiments. The apparent increase in stroke volume after digitalis is therefore not here significant. Apart from the association again of signs of cardiac insufficiency and a low C.R. and the failure either of these signs to clear up or the C.R. to increase with the therapeutic measures adopted, this case is interesting because after the digitalis she developed a pulsus bigeminus. Three determinations were made while the pulse was

bigeminal/

bigeminal and a fourth after normal rhythm had been resumed, and no significant change in C.R. was noted. Apparently, therefore, during bigeminy the presumably deficient output of the extra systole is counter-balanced by an increased output at the normal beat. At one period the rhythm was liable to change frequently from normal to bigeminy and vice versa, and from counts made at these change-overs it was determined that no change in the heart rate occurred. This is consistent with the fact that the assumption of bigeminal rhythm has no effect on the cardiac output.

Of the next two cases the one, Mrs T., with auricular fibrillation had no symptoms suggestive of any degree of cardiac failure while the other, T. McN., who had a myocarditis secondary to chronic bronchitis and emphysema became dyspnoeic on even moderate exertion. Mrs T. in three estimations before digitalis had an average C.R. of 5.4 L. and a S.V. of 52 cc. During the week after digitalis there was a drop in the average C.R. to 4.1 L., but since the heart rate fell from 105 to 68 the output per beat rose slightly to 60 cc. The lowest C.R. was that on the day after the giving of the digitalis and nausea may partly account for it, but it cannot account for the result of the next determination which is also low.
T. McN. had also a C.R. coming into the lower limits of the normal range, averaging before digitalis 5.1 L. with/

with, on account of the rapid heart rate, a relatively small S.V. - 51 cc. Digitalis produced no significant effect in this case.

There follow three cases resembling one another closely in their history and clinical condition. All young girls, each had had a very definite acute rheumatic carditis and each was past the acute stage. In all there was definite involvement of the mitral valve, the physical signs suggesting the presence of both stenosis and incompetence. In each of these cases the C.R. is within normal limits, but in K.G. and E.B. the S.V. tends to be low, the C.R. being maintained by a rapid heart rate.

In F.K. in whom the valvular lesion was presumably of the longest standing, there being a history of acute rheumatism with cardiac involvement 10 years before, the C.R. is surprisingly high; the lowest value noted was 6.4 litres. This is especially surprising in view of the fact that this patient had been confined to bed for 8 months. Excitement appeared to have a very marked effect on the C.R. in this case. During the determinations on 22.2.27 and 2.3.27 which resulted in the high C.R. figures of 12.6 and 10.9 litres, she was for some reason, quite markedly excited. The increase in C.R. on both these occasions was due entirely to increase in S.V., the heart rate remaining at its usual level.

A/

A similar increase in C.R. due entirely to increase in S.V. was noted in Mrs D. when however it appeared to be due to restlessness rather than excitement.

A dose of digitalis was given to K.G. while she was under observation, and appears to have caused an increase in C.R., but as only one estimation of the resting C.R. was done before the digitalis was given, definite conclusions as to its effect cannot be made.

In this patient and in one other, D.C., a case of complete heart block, observations were attempted on the effect of exercise on the C.R. In the first experiment in each case, as will be seen from the tables, there was immediately after exercise an increase in heart rate, C.R. and S.V., as was expected, and half an hour later these functions had decreased in the first case almost to and in the second, below the initial level. In the second experiments the fallacy underlying repeated estimations of C.R. at short intervals by the ethyl iodide method was made apparent. In D.C. the initial value of the C.R. on 27.1.27 was 5.0 L., high because of an insufficient period of rest. After moderate exertion the C.R. rose to 5.7 L., the increase being due entirely to increase in S.V.- a possible enough finding. After thirty minutes rest the C.R. had apparently fallen to 3.3 litres and now severe exertion only increased it to 4.3 litres, a value not only lower than/

than that obtained after mild exercise but even lower than the initial result - a finding obviously not true. This progressive fall in the C.R. figures obtained from consecutive observations done at short intervals was also noticed by Davies and Gilchrist[33]. It appears to be due either to a pharmalogical effect of the ethyl iodide which produces a real diminution in C.R. or to an accumulation of ethyl iodide in the venous blood causing an increase in the concentration of the gas in the expired and alveolar air samples, and consequently an apparent fall in C.R. Whatever the explanation, this fallacy precludes any conclusions being drawn from the results of such experiments as those quoted - a peculiarly unfortunate limitation in the method.

The next four cases had each an incompetence of the aortic valve due in the first to a rheumatic endocarditis, and in the other three to a syphilitic aortitis amounting in the last case to a definite aneurysm. In none of these cases is the C.R. low, the lowest values being those obtained in R.M. who peculiarly enough had fewer signs of cardiac insufficiency than the other three. In W.R. the C.R. and S.V. are both surprisingly large considering that this man was unable for more than moderate exertion on account of breathlessness. It is possible that another factor enters into this case for the man looked/

looked pale and anaemic; unfortunately the haemoglobin was not estimated. Both R.N. and W.R. were examined as out-patients, thirty minutes rest on the couch being taken before a determination was made, and while the results from W.R. agree closely, those from R.N. show more divergence than is usual.

The observations made on the three cases of complete heart block are especially interesting since no other record of the C.R. in heart block has been found in the literature. In each case the S.V. is large, especially in G.J. and J.B. In the first two cases who showed little evidence of cardiac insufficiency a C.R. at or just below the lower level of the normal range is maintained. The third case, whose circulation clinically was much less efficient, had a C.R. of only 3.2 L.

Unfortunately only one observation was possible on each of two of these cases.

Mrs D. Age 32. Wt. 59-51 Kg. Mitral Incompetence. Cardiac Failure.

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index. c.c. per kilo.	Resp. Volume. Litres per min.	Alv. CO_2.	Oxygen Consumpt. c.c. per min.	R.Q.	Art.Ven. O_2 diff. Vols %	Remarks.
2.12.26	102	2.7	27	.48	13.35	3.27%	324	.93	11.99	
" " "	102	2.5	24	.43	14.1	3.26%	382	.79	15.29	
4.12.26	96	2.5	27	.48	14.4	-	-	-	-	No correction for
5.12.26	Digitalis 1.7 G in 3 dozes. Nausea, no vomiting.									temperature & pressure
6.12.26	71	3.0	43	.76	9.05	3.8%	303	.79	10.1	10 a.m.
" " "	66	3.3	49	.87	9.05	3.7%	279	.76	8.46	2.30 p.m.
8.12.26	74	3.2	43	.76	9.7	-	294	.89	9.19	
11.12.26	90	4.6	52	.92	11.5	3.95%	329	.95	7.15	
24.12.26	Discharged.									
10.1.27	Readmitted.									
12.1.27	Digitalis 1.7 G in 3 doses. Vomited part of first dose.									
13.1.27	75	4.8	63	1.15	7.54	-	-	-	-	10 a.m.
" " "	62	3.2	52	.95	6.91	4.33%	216	.89	6.8	2.30 p.m.
17.1.27	90	4.1	45	.82	10.19	-	-	-	-	
18.1.27	85	4.5	54	.98	10.81	4.11%	316	.92	7.1	
25.1.27	93	2.6	28	.51	10.84	-	-	-	-	
" " "	89	3.0	34	.62	9.54	3.64%	267	.89	8.9	

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index. c.c. per kilo.	Resp. Volume. Litres per min.	Alv. CO_2.	Oxygen Consumpt. c.c. per min.	R.Q.	Art.Ven. O_2 diff. Vols.%	Remarks.
26.1.27	98	2.8	28	.51	10.83	3.47%	-	-	-	
" " "	92	3.1	34	.62	9.83	3.48%	248	.94	8.0	
27.1.27	Digitalis 1.8 G in 8 doses at 6 hourly intervals.						Marked nausea and frequent vomiting.			
28.1.27	69	3.6	51	.93	8.87	4.66%	254	.93	7.06	
29.1.27	66	3.6	54	.98	8.71	4.05%	260	.88	7.20	
1.2.27	82	3.5	42	.76	12.13	3.76%	-	-	-	
3.2.27	80	4.6	57	1.04	11.63	3.73%	290	1.08%	6.3	2.30 p.m. Restless.
7.2.27	98	3.4	34	.62	10.64	3.93%	-	-	-	
8.2.27	84	3.4	40	.73	9.67	-	378	.64	11.12	
11.2.27	100	4.3	43	.78	10.6	4.02%	378	.75	8.79	Lying flat. Excited.
14.2.27	91	3.2	35	.64	8.38	4.19%	285	.79	8.9	
14.2.27	Digitalis 1.7 G in 3 doses. Marked nausea after last dose.						Vomited once.			
16.2.27	59	5.6	95	1.73	7.37	3.57%	252	.73	4.5	Dropping beats. Sino Auricular Block.
18.2.27	65	4.6	71	1.29	9.68	3.96%	289	.76	6.28	
26.2.27	76	6.1	80	1.45	10.2	4.32%	310	.97	5.0	
28.2.27	85	5.4	64	1.16	10.5	4.53%	348	.91	6.44	
2.3.27	81	4.6	57	1.04	9.08	4.43%	239	.97	5.02	
2.3.27	Digitalis 1.7 G in 3 doses. Nausea and vomiting.									
4.3.27	83	3.8	46	.84	7.98	4.39%	235	.87	6.02	

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume. Litres per min.	Alv. CO_2.	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols. %	Remarks.
5.3.27	68	3.5	51	.93	7.64	4.14%	287	.64	8.02	
9.3.27	72	4.1	57	1.04	9.72	4.42%	-	-	-	
11.3.27	75	4.8	64	1.16	9.72	4.68%	-	-	-	
21.3.27	82	4.5	55	1.00	9.3	4.44%	-	-	-	
22.3.27	78	5	64	1.16	9.4	4.33%	316	.8	6.32	
22.3.27	Digitalis 1.3 G in 5 doses. No nausea or vomiting.									
24.3.27	71	7.3	102	1.86	8.8	4.58%	312	.74	4.28	
26.3.27	88	6.9	79	1.44	9.04	4.76%	-	-	-	
6.4.27	90	4.8	53	.96	9.51	4.35%	-	-	-	
11.4.27	90	4.7	52	.95	10.48	-	290	.87	6.17	
11.4.27	Digitalis 1.3 G in 5 doses. No nausea or vomiting.									
13.4.27	79	7.4	94	1.71	10.4	4.17%	262	1.14	3.54	Disturbed by noisy valve
14.4.27	82	4.9	59	1.35	9.73	4.48%	283	.97	5.78	

Mrs S. Age 55. Wt. 36 Kg. Auricular Fibrillation. Cardiac Failure.

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume. Litres per min.	Alv. CO_2	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols. %	Remarks.
14.2.27	200±	4.1	21	.58	8.15	-	279	.8	6.80	Very restless.
" " "	200±	3.5	18	.5	8.39	4.11%	288	.79	8.20	Heart Rate from
15.2.27	200±	3.8	19	.53	7.91	4.14%	308	.71	8.10	Electrocardiogram.
" " "	200±	3	15	.41	7.34	4.12%	245	.75	8.17	Uncountable otherwise.
15-16.2.27	Digitalis 1.2 G in 3 doses. No nausea or vomiting.									
16.2.27	90±	6.4	71	1.97	6.34	3.98%	240	.8	3.75	
18.2.27	88±	6.7	78	2.16	5.86	4.68%	241	.73	3.60	
23.2.27	135±	6.3	47	1.31	6.03	4.8%	240	.91	3.81	
2.3.27	114±	5.7	50	1.39	6.66	4.7%	251	.71	4.40	
3.3.27	103±	5.8	57	1.58	7.39	-	282	.8	4.86	3.30 p.m.
5.3.27	111±	4	36	1.00	6.86	5.02%	248	.85	6.2	Not feeling well. Breathless.
8.3.27	101±	5.5	54	1.5	6.69	4.97%	-	-	-	
9.3.27	Digitalis 1.1 G. Marked nausea.									
10.3.27	83±	3.4	41	1.14	5.87	-	-	-	-	Feeling of nausea.
17.3.27	110±	6.1	56	1.56	8.05	4.66%	-	-	-	

J.H. Age 63. Female. Wt. 73.5 Kg. Auricular Fibrillation.

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume. Litres per min.	Alv. CO_2	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols. %	Remarks.
22.2.27	102±	4.8	47	.64	7.67	4.43%	269	.74	5.60	
23.2.27	95±	4.6	49	.67	7.37	4.16%	252	.71	5.48	
26.2.27	90±	4.6	51	.89	8.18	4.37%	286	.86	6.22	
10-11.2.27	Digitalis 2.4 G in 3 doses. Excessive nausea and vomiting.									
10.3.27	103±	4.2	40	.54	7.32	4.48%	-	-	-	
16.3.27	79±	4.6	59	.80	7.02	-	-	-	-	
18.4.27	Readmitted.		Cardiac Failure.							
19.4.27	140±	2.5	18	.25	9.45	3.81%	250	.81	10.0	Orthopnoeic.
20.4.27	157±	3.6	23	.31	12.39	3.46%	240	.88	6.67	Very distressed. Slightly cyanosed.
20-21.4.27	Digitalis 1.8 G in 5 doses. No nausea or vomiting.									
22.4.27	80±	4.3	54	.73	7.75	3.63%	174	.89	4.05	
23.4.27	84±	4.1	48	.65	9.68	3.6%	264	.76	6.44	
3.5.27	95±	3.9	41	.56	8.42	3.54%	268	.71	6.87	
8.5.27	101±	3.7	37	.50	7.66	4.09%	257	.75	6.95	
12.5.27	110±	3.5	31	.42	7.9	3.97%	261	.74	7.46	

J.D. Age 16. Female. Wt. 35.5 Kg. Aortic Stenosis & Incompetence. Cardiac Failure.

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume. Litres per min.	Alv. CO_2	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols. %	Remarks.
18.4.27	103	3.0	29	.76	8.65	3.8%	257	.74	8.57	
19.4.27	97	2.1	21	.55	7.22	4.41%	183	.91	8.71	
20.4.27	94	2.2	24	.63	7.11	3.88%	176	.83	8.00	
21-22.4.27	Digitalis 1.1 G in 5 doses.				No nausea or vomiting.					
23.4.27	82	2.5	30	.79	6.68	4.32%	176	.96	7.04	Bigeminy.
25.4.27	83	2.2	26	.68	6.66	4.44%	176	.93	8.00	Bigeminy.
27.4.27	84	2.9	35	.92	7.03	4.52%	236	.84	8.14	Bigeminy.
30.4.27	83	2.2	27	.71	6.55	4.16%	221	.81	10.05	Regular
Mrs T. Age 68. Wt. 67.5 Kg. Auricular Fibrillation.										
1.3.27	108	5.8	54	.80	6.86	4.28%	272	.74	4.60	
2.3.27	95	5.3	56	.83	5.97	4.3%	219	.66	4.13	
3.3.27	112	5.0	45	.67	6.84	4.75%	263	.81	5.26	
3-4.3.27	Digitalis 2.2 G in 3 doses. Nausea & vomiting for 24 hrs. after last dose.									
4.3.27	74	3.4	46	.68	5.73	4.76%	234	.72	6.88	
7.3.27	62	3.9	63	.93	5.37	5.26%	230	.74	5.90	
10.3.27	69	5.0	72	1.08	6.05	5.06%				

T. McN. Age 61. Male. Wt. 56 Kg. Myocarditis.

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume. Litres per min.	Alv. CO_2	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols. %	Remarks.
30.3.27	90	4.7	52	.93	9.34	4.67%	281	.89	5.98	Occasional extra-systoles.
1.4.27	110	5.4	49	.88	11.95	4.69%	314	.97	5.81	2.30 p.m.
4.4.27	101	5.3	53	.95	11.6	4.65%	296	1.0	5.58	3 p.m. Expiratory wheezing
5-6.4.27	Digitalis 1.8 G. in 5 doses.				No nausea or vomiting.					
6.4.27	95	5.6	58	1.04	9.58	4.84%	-	-	-	
8.4.27	91	3.9	43	.77	9.33	-	255	.96	6.54	
12.4.27	82	5.6	68	1.21	9.43	4.17%	257	.9	4.59	

(Imm. = immediately)

K.G. Age 17. Female. Wt. 61 Kg. Mitral Stenosis and Incompetence.

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume. Litres per min.	Alv. CO_2	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols. %	Remarks.
18.1.27	92	4.9	53	.87	6.84	5.19%	272	.78	5.55	2 p.m. Resting.
" " "	115	7.9	68	1.11	14.39	4.29%	340	1.2	4.30	4.30 2.30 p.m. Imm. after exercise.
" " "	97	6.2	64	1.05	7.35	5.19%	307	.68	4.95	3 p.m. 30 mins. after exercise.
18-21.1.27	Digitalis 2 G. 8 doses at 6 hrly. intervals. Marked nausea and frequent vomiting.									
19.1.27	73	5.0	68	1.11	7.25	5.3%	262	.87	5.24	2.30 p.m.
" " "	74	5.0	68	1.11	7.10	-	-	-	-	3 p.m.
21.1.27	83	5.6	67	1.10	5.86	5.87%	270	.78	4.82	
24.1.27	79	6.4	81	1.32	6.29	6.0%	275	.87	4.30	
25.1.27	83	7.3	88	1.44	6.65	-	284	.91	3.89	2.15 p.m. 10 mins. rest only.
" " "	96	6.7	70	1.15	10.6	5.63%	369	1.05	5.51	2.45 p.m. Imm. after exercise.
" " "	87	6.4	74	1.21	6.92	5.99%	293	.89	4.58	3.15 p.m. 30 mins. after "
28.1.27	90	5.1	56	.92	6.60	5.55%	244	.81	4.78	

F.K. Age 24. Female. Wt. 51.5 Kg. Mitral Stenosis and Incompetence.

Date	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume. Litres per min.	Alv. CO_2	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols. %	Remarks.
22.2.27	78	12.6	162	3.15	8.11	3.46%	273	.9	2.17	Excited.
23.2.27	73	7.5	103	2.0	7.73	-	279	.9	3.72	
24.2.27	73	7.7	105	2.04	6.15	5.4%	213	.86	2.77	
2.3.27	79	10.9	138	2.67	5.45	4.34%	238	.78	2.18	Excited. Pulse irregular.
5.3.27	75	6.4	85	1.65	6.45	4.79%	275	.84	4.30	
9.3.27	89	6.7	75	1.46	6.43	5.1%	-	-	-	
17.3.27	97	6.9	70	1.36	4.89	-	-	-	-	
	E.B. Age 16. Female. Wt. 41.8 Kg.				Mitral Stenosis and Incompetence.					
4.2.27	100	5.4	54	1.29	6.23	5.05%	211	.99	3.91	
22.2.27	95	5.5	57	1.36	5.00	-	242	.79	4.40	
	Mrs F.D. Age 22. Wt. 44.5 Kg.				Aortic Incompetence.					
10.2.27	74	6.6	89	2.0	5.89	4.84%	300	.71	4.55	
16.2.27	78	7.2	93	2.09	5.88	5.93%	296	.62	4.11	
	R.N. Age 49. Male. Wt. 68 Kg.				Aortic Incompetence.					
29.3.27	82	6.2	75	1.10	10.35	4.41%	295	.8	4.76	30 mins. rest on couch.
" " "	82	5.8	70	1.03	8.15	5.06%	-	-	-	
31.3.27	76	4.6	60	.88	9.23	4.48%	285	.87	6.20	" " "
" " "	76	4.3	57	.84	8.63	4.66%	280	.81	6.51	

(Imm. = immediately)

W.R. Age 57. Male. Wt. 53 Kg. — Aortic Incompetence.

Date.	Heart Rate per Min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume. Litres per min.	Alv. CO_2	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols.%	Remarks.
14.4.27	68	7.7	113	2.13	6.20	4.98%	229	.91	2.97	30 mins. rest on couch.
28.4.27	71	8.2	116	2.19	6.42	4.89%	243	.79	2.95	" "
" " "	69	7.8	113	2.13	5.39	4.26%	204	.83	2.62	" "
	M. McD. Age 30. Male. Wt. 46 Kg.				Aortic Incompetence.		Aortic Aneurysm.			
30.4.27	94	6.2	66	1.43	7.61	4.52%	282	.87	4.55	
4.5.27	104	6.1	59	1.33	9.80	4.49%	314	1.0	5.15	
	D.C. Age 64. Male. Wt. 73 Kg.				Complete Heart Block.		Aortic Incompetence.			
10.1.27	39	4.4	113	1.55	8.75	-	-	-	-	
" " "	36	4.1	115	1.58	7.20	4.62%	249	.78	6.07	
20.1.27	37	5.4	147	2.01	7.09	5.19%	244	.81	4.52	10 a.m. 10 mins. rest only.
	41	7.1	173	2.37	13.66	4.27%	352	1.16	4.96	10.40 a.m. Imm. after exercise.
	37	4.2	113	1.55	7.76	5.17%	248	.86	5.90	11.10 a.m. 30 mins. after exercise.
27.1.27	37	5.0	134	1.84	7.18	4.86%	235	.91	4.70	10 a.m. 10 mins. rest only.
	36	5.7	159	2.18	8.71	4.43%	280	.98	4.91	10.25 a.m. Imm. after slight exercise.
	39	3.3	86	1.18	8.48	4.61%	254	.93	7.60	10.55 a.m. 30 mins. rest. Uncomfortable.
	39.	4.3	111	1.52	13.8	4.61%	371	1.1	8.63	11.15 a.m. Imm. after more severe exercise.

G.J. Age 45. Male. Wt. 50.5 Kg. Complete Heart Block.

Date.	Heart Rate per Min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume. Litres per min.	Alv. CO_2.	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols. %.
7.1.27	36	5.5	154	2.8	8.28	5.16%	277	.90	5.04

J.B. Age Male. Wt. 74.5 Kg. Complete Heart Block.

26.5.27	21	3.2	151	2.03	7.65	4.25%	249	.83	7.78

CASE HISTORIES.

Mrs D.

Aged 32. Cook. No children.

Complaints. Palpitation especially at nights for $3\frac{1}{2}$ years.

Dyspnoea on exertion for $2\frac{1}{2}$ years.

Occasional oedema of ankles for 6-8 months.

Previous Health. Miscarriages 8 & 7 years ago.

Panhysterectomy 5 years ago.

Acute rheumatism 2 years ago:

no other rheumatic history.

Wassermann reaction negative.

Admitted 27.4.26. Moderate cardiac failure with oedema.

Pulse regular. B.P. $\frac{140\text{-}150}{90\text{-}100}$.

Heart enlarged. $\frac{111}{1"/7"}$ in 6th L. space.

Blowing mitral systolic murmur propagated into axilla. Same systolic murmur audible in all other areas. No diastolic or presystolic murmur in any area.

2nd sound accentuated in pulmonary area.

Treatment: rest in bed; digitalis.

Discharged 1.6.27.

Readmitted 20.11.26. Marked dyspnoea and cyanosis on exertion.

Slight oedema. Physical exam. and treatment as before.

Discharged/

Discharged at own request 14.12.26.

Readmitted 10.1.27. having collapsed in street.

Praecordial pain and palpitation. Slight oedema only. Physical examination as before.

Treatment as before.

Discharged 14.5.27.

Electro-cardiogram. Normal rhythm; slight increase in P.R. interval.

After digitalis marked increase in P.R. interval and after one dose sino-auricular block.

No evidence of ventricular preponderance.

Diagnosis. Mitral Incompetence with ? Stenosis.

Cardiac Failure.

Mrs S.

Age 55. Housewife. 5 children.

Complaints. Extreme breathlessness on exertion, oedema of ankles at night and gastric symptoms.

Several years duration.

Previous Health. No history of acute rheumatism or scarlet fever.

Appearance suggestive of past hyperthyroidism.

W.R. - .

Admitted 12.2.27. Pulse rate about 100-120 extremely irregular. Actual heart rate uncountable, but pulse deficit large, probably 80-100.

Marked venous pulsation in neck.

Heart/

Heart dilated $\frac{111}{1"/5"}$ in 5th L. space.

No bruits detected even when heart rate slowed.

No oedema.

Electrocardiogram. Auricular fibrillation.

Ventricular rate 200 per min. before 1st dose of digitalis.

Treatment. Rest in bed and digitalis.

Diagnosis. Auricular Fibrillation.

Cardiac failure.

J.H.

Female, unmarried. Age 63. Cook.

Complaints. Dyspnoea, palpitation and occasional praecordial pain on exertion. Occasional oedema of ankles - 12 months duration.

Previous Health. Acute rheumatism 3 years ago. Occasional sore throats when younger. Chronic winter cough for some years - worst during past winter.

Admitted 19.2.27. with Acute bronchitis. Irregular pulse with pulse deficit on admission which disappeared after 2-3 days rest in bed.

Heart $\frac{111}{1"/4\frac{1}{2}"}$ in 5th space. No bruits audible. Sounds difficult to hear.

Electrocardiogram. Auricular Fibrillation.

Treatment. Rest in bed. Symptomatic. Digitalis.

Diagnosis. Auricular Fibrillation. Chronic Bronchitis and **Emphysema.**

Readmitted. Extremely distressed, cyanosed, orthopnoeic.

Heart /

Heart rate 150 ± fibrillating; pulse deficit 50±

Treatment. Rest in bed with digitalis.

J.D.

Female. Age 16. At home.

During past 8 weeks attacks of praecordial pain on exertion and during night. Attacks of breathlessness during night. Cough and on one occasion small haemoptysis.

Scarlet Fever aged 8. No other illnesses. W.R. - .

Pulse regular. B.P. $\frac{90}{60}$.

Heart enlarged $\frac{111}{1"/5"}$ in 6th space. No thrills.

Mitral area. Systolic murmurs prop. into axilla.

Diastolic murmur occasionally audible.

Aortic area. Rough systolic murmur prop. into neck. No diastolic heard.

Electrocardiogram . Pulsus Bigeminus after digitalis.

Treatment. Rest in bed: digitalis.

Diagnosis. Aortic Stenosis and Incompetence; Mitral Incompetence.

1.7.27. Died. P.M. Aortic Stenosis and incompetence. No disease of mitral valve. No recent vegetations. Myocardium extremely flabby.

Mrs T.

Age 68. Housewife. Two children.

Complaints. Pain and frequency of micturition: vaginal discharge (carcinoma of body of uterus).

No/

No symptoms relative to circulatory system.

No rheumatic history. W.R. - .

Pulse totally irregular: little or no pulse deficit.

Heart not enlarged. No bruits. Second sound reduplicated in all areas.

Electrocardiogram. Auricular fibrillation. Form of ventricular complexes suggestive of an arborisation block.

Treatment. Rest in bed, digitalis. Transferred for radium therapy.

Diagnosis. Auricular Fibrillation. Carcinoma Corporis Uteri.

T. McN.

Male. Age 61. Labourer. Ex-soldier.

Complaints. Cough, increasing shortness of breath on exertion - 12 months duration.

Previous History. Fairly frequent bronchitis.

W.R. - .

Before and on admission very numerous extra systoles which cleared after a few days in bed.

Arterial wall thickened and tortuous. B.P. $\frac{140}{80}$.

Heart $\frac{111}{\frac{1}{2}"/3"}$ in 5th L. space. Left mitral systolic bruit.

Electrocardiogram. Extra systoles, auricular in origin.

Treatment. Rest in bed, symptomatic; digitalis.

Diagnosis. Chronic bronchitis and emphysema.

Myocarditis.

K.G.

Female. Age 17. Shop assistant.

Previous Health. Chorea 4 years ago. W.R. - .

Admitted 3.6.26. with chorea. Mitral systolic and presystolic murmurs with accentuated pulmonary 2nd sound.

Heart not enlarged.

Developed pericarditis while in Ward.

Discharged 14.9.26.

Readmitted 31.12.26. for rest and observation.

Cardiac condition as on 1st admission.

Diagnosis. Mitral Stenosis and Incompetence.
Rheumatic Carditis.

F.K.

Female. Age 24. Typist.

Previous Health.

Acute rheumatism and pericarditis aged 13.

Pneumonia followed by heart block aged 14.

W.R. - .

Admitted 29.12.26. having been in bed at home 6 months following an attack of acute rheumatism.

Occasional praecordial pain and palpitation even in bed.

Pulse rapid 90-110. Regular.

Heart enlarged $\frac{111}{1''/6''}$ in 5th L. space.

Loud blowing systolic murmur in mitral area prop. into axilla. Pulmonary second reduplicated.

Electrocardiographic/

Electrocardiographic exam. Increase in P.R. interval; this greatly exaggerated after digitalis.

Diagnosis. Mitral Stenosis and Incompetence.
Rheumatic Carditis.

E.B.

Female. Age 16. Domestic Servant.

Previous Health. Nil of note.

Admitted 30.10.26. with acute rheumatism.

Developed pericarditis while in Ward and also a pleurisy. Joint pains showed tendency to become subacute.

Pulse regular. B.P. $\frac{110}{80}$.

Heart $\frac{111}{\frac{1}{2}" / 4\frac{1}{2}"}$ in 5th space.

Mitral Area. Systolic murmur prop. into axilla.

Definite mid diastolic murmur.

Pulmonary 2nd sound accentuated.

Diagnosis. Rheumatic Carditis.
Mitral Stenosis and Incompetence.

Mrs F.D.

Age 22. Housewife. One child.

Previous Health. Frequent sore throats, tonsils large and septic. W.R. - .

Palpitation and breathlessness moderately easily induced by exertion for 5 years past and this more marked since child born 9 months ago. Now again $3\frac{1}{2}$ months pregnant.

Pulse./

Pulse. Large excursion B.P. $\frac{140}{60}$.

Heart, not enlarged $\frac{111}{\frac{1}{2}" / 3\frac{1}{2}"}$ in 5th L. space.

Systolic and diastolic bruits originating in aortic area.

Electrocardiogram. Nil abnormal showing.

Diagnosis. Aortic Incompetence (rheumatic).

R.N.

Male. Age 49. Carter.

Admitted with complaint of abdominal pain. No definite circulatory symptoms.

W.R. +++

Pulse. Corrigan. B.P. $\frac{140}{40}$.

Heart enlarged $\frac{111}{\frac{1}{2}" / 4"}$ in 6th space.

Systolic and diastolic aortic murmurs.

Diagnosis. Aortic Incompetence.
Syphilitic Aortitis.

W.R.

Male, aged 57. Packer.

Previous Health. W.R. +++ .

Symptoms. Breathlessness and occasional praecordial pain on exertion for 12 months. Occasional oedema of feet for 6 months. Looked anaemic.

Pulse. Corrigan B.P. $\frac{130}{35}$.

Heart enlarged $\frac{111}{\frac{1}{2}" / 5\frac{1}{2}"}$ in 6th L. space.

Systolic and Diastolic murmurs originating in aortic area.

Electrocardiogram. Definite left sided preponderance.

Diagnosis. Aortic Incompetence.
Syphilitic Aortitis.

M. McD.

Male. Age 30. Miner.

Admitted 10.12.25 complaining of pain in chest, hoarseness and dyspnoea on exertion. W.R. + .

Pulses equal and synchronous. B.P. $\frac{120}{60}$.

Well marked pulsation 2nd right intercostal space.

Heart $\frac{111}{1\frac{1}{2}"/4"}$ in 5th L. space. Aortic systolic and diastolic murmurs.

Increase in transverse dullness across manubrium.

Tracheal tug very well marked. Definite X-ray evidence of aneurysm involving arch of aorta.

Readmitted. Same physical signs and symptoms.

Electrocardiogram. Normal Rhythm. Left ventricular preponderance.

Diagnosis. Aortic Aneurysm.

Aortic Incompetence.

D.C.

Male. Age 64. Warehouseman.

Previous health. ?Syphilis 39 years ago. W.R. - .

Breathless only on moderate exertion. No cardiac pain. No fits. No oedema.

Pulse rate 36. Corrigan. B.P. $\frac{240}{60}$.

Heart enlarged $\frac{111}{\frac{3}{4}"/5\frac{1}{2}"}$ in 6th L. space.

Aortic systolic and diastolic murmurs.

Electrocardiogram. Complete dissociation of auricular and ventricular complexes.

Diagnosis. Complete Heart Block.

Aortic Incompetence.

G.J.

Male. Age 45. Railway guard.

Previous history. Nil to note.

W.R. - .

Complaints. Attacks of giddiness. No oedema.

No marked dyspnoea on exertion.

Pulse rate 36.

Heart not enlarged $\frac{111}{\frac{1}{2}" / 3\frac{3}{4}"}$ in 5th L. space.

Sounds closed all areas.

Electrocardiogram. Complete dissociation of auricular and ventricular complexes.

Diagnosis. Complete Heart Block.

J.B.

Male. Age 68. Rubber-worker.

"Giddy turns", occasionally associated with loss of consciousness, repeatedly during last 2 years.

Increasing breathlessness on exertion for two years.

No oedema.

History of gonorrhoea at age of 18. W.R. - .

Cyanotic tinge in lips.

Pulse extremely slow - 21 per minute - regular.

B.P. $\frac{205}{95}$.

Heart $\frac{111}{1" / 4\frac{1}{4}"}$ in 5th L. space. Heart rate 21 per min. Mitral systolic murmur propagated towards axilla. Other sounds closed.

Electrocardiogram. Complete heart block. Left sided ventricular preponderance.

Diagnosis. Complete Heart Block.

DISCUSSION.

Effect of Valvular Lesions on Circulation Rate.

In a mechanical pumping system a leaky or unduly resistant valve will diminish the efficiency of the system and will reduce the output unless the pumping force is increased. In the same way it would be expected that an incompetent or stenotic valve would tend to reduce the output of the heart unless the handicap were in some way compensated for.

In the six cases of aortic incompetence examined the circulation rates (table 10) are with two exceptions within normal limits. In one of these cases (D.C.) in whom the C.R. - 4.1 litres, might be regarded as low, there is the complication of a complete heart block. This is of interest in view of the old clinical teaching that a rapid heart rate is of advantage in aortic incompetence as tending to lessen regurgitation by shortening diastole. The apparent support given to this by these results is modified

Case.	H.R.	C.R.	S.V.	S.I.	A.V. O_2 Diff.
Mrs F.D.	76	6.9	91	2.05	4.33
R.B.	79	5.2	65	.96	5.82
W.R.	69	7.9	114	2.15	2.85
M. McD.	99	6.15	62.5	1.38	4.85
D.C.	37.5	4.25	114	1.57	6.07
J.D.	98	2.4	25	.65	8.43

TABLE 10. Aortic Incompetence.

modified by the fact that the C.R. maintained at rest, though low according to the rather arbitrary standard adopted, was yet apparently sufficient for the patients needs and could be increased on exertion to at least 7.1 litres, the ventricular rate not increasing beyond an average of 41.

In the other, J.D., the C.R. was definitely low and remained low, - 2-3 litres - while the patient was under observation. Here there was definite stenosis as well as incompetence at the aortic valve, and the heart muscle as seen post-mortem was extremely flabby. In view of this condition of the myocardium the low C.R., cardiac failure, and subsequent death of the patient, cannot be attributed entirely to the actual valvular lesion.

The normal C.Rs. found in the other four cases are in accord with the results obtained by other workers in cases of aortic incompetence.

In the three cases of mitral stenosis observed the C.Rs. (table 11) are also within normal limits though in two this is only maintained by a rapid heart rate, the output per beat being small. This /

Case.	H.R.	C.R.	S.V.	S.I.	Art. Ven. O_2 Diff.
K.G.	91	5.0	55	.9	5.17
F.K.	81	7.04	88	1.70	3.6
E.B.	98	5.45	56	1.33	4.16

TABLE 11. Mitral Stenosis.

This differs from the results of other workers who describe a decrease in both S.V. and C.R. in mitral stenosis. In none of the three cases here examined, however, was the stenosis clinically well marked, being the result presumably of an endocarditis of fairly recent origin; while in those other cases reported, certainly those of Meakins and Fetter, the lesion was much more advanced. If, as would seem possible, the C.R. is decreased in the more marked cases of stenosis but not in the early ones, it still remains an open question as to how much this decrease is due to the narrowing of the mitral orifice and how much to associated myocardial damage.

In such a case as Mrs D. the low C.R. which she at times showed was obviously not directly caused by the incompetence of her mitral valve, for the C.R. increased on adoption of measures which, though they might increase the power of the myocardium, could in no way affect the condition of the valve.

From a consideration of the results here reported, and of those of other observers, it would appear that valvular lesions, with the possible exception of well marked stenoses, are not associated with any decrease in C.R. so long as the myocardium remains efficient. In such cases, however, the strain on the myocardium must be greater than that in hearts with efficient valves. Hearts with valvular lesions are probably

especially/

especially liable therefore to myocardial failure, and when this has developed the C.R. will be low (cf. J.D. and Mrs D.).

The Effect of Irregularities in Cardiac Rhythm on the Circulation Rate.

Three cases of auricular fibrillation were examined but in none, unfortunately, was it possible to compare the C.R. in fibrillation and in normal rhythm. In the case reported by Meakins the C.R. during normal rhythm was higher than when the heart was fibrillating. Before being accepted this observation would require confirmation, - more especially as most patients are conscious of no benefit following the restoration of normal rhythm with quinidine, which is not as would be expected if the C.R. were thereby increased. There is a possibility that the increase observed may not have been due to the restoration of normal rhythm, but to the digitalis which presumably was given before the quinidine.

Two of the three cases here investigated were observed at periods when there were no marked signs of cardiac failure and when the heart was not under the influence of digitalis. The average C.Rs. then in those two cases were just at the lower border of the normal range, 4.7 and 5.4 litres, the S.Vs. being rather/

rather small, 50 and 52 cc. As there was little or no pulse deficit in either of these cases during the period in question, that factor has not entered into the production of the low S.V.

Two of the cases, Mrs S. and J.H. were observed when the ventricular rhythm was very rapid - 200 per minute in Mrs S.- and in each case this was associated with a low C.R. and definite signs of cardiac failure. It would appear probable, on the analogy of the decrease in C.R. which occurs in dogs during experimental irregular tachycardia, that the tachycardia in these two cases, especially in Mrs S., was itself, at least to some extent, responsible for the low C.R. A possible element of myocardial weakness has however also to be taken into account. The gradual decline in the C.R. in J.H. towards the end of the period of observation was not associated with any marked increase in ventricular rate and was almost certainly due to decreasing myocardial power. This decrease in the C.R. which apparently may occur in auricular fibrillation with the development of a rapid ventricular rate, may to some extent explain the frequency and the occasional suddenness with which gross cardiac failure develops in these cases, and also why they usually respond so well to digitalis.

It has already been noted (p.p. 78) that in J.D. the bigeminy which developed after digitalis did not affect/

affect the C.R., the output of the normal beat apparently being increased to make up for any deficiency in the output of the extra systole.

The Circulation in Complete Heart Block.

With the ventricles maintaining their own inherent slow rhythm, the maintenance of a sufficient rate of blood flow in complete heart block must depend on a large output per beat. In two of the three cases of complete heart block investigated (table 12) a fairly efficient circulation was maintained, the S.Vs in these two cases, one further handicapped by an aortic incompetence, being high.

Case.	H.R.	C.R.	S.V.	S.I.	Art. Ven. O_2 diff.
D.C.	37.5	4.25	114	1.57	6.07
G.J.	36	5.5	154	2.8	5.04
J.B.	21	3.2	151	2.03	7.78

TABLE 12. Complete Heart Block.

In the third case, whose ventricular rate was only 21 per minute, despite a S.V. of 150 cc., a C.R. of only 3.2 litres was attained. With so slow a ventricular rate a S.V. of 200 cc. would be required to maintain a C.R. of 4.2 litres. That hearts whose myocardium is presumably damaged can compass so large a/

a S.V. as those here noted is probably due to the long recovery period which the ventricular muscle gets during diastole.

These cases show that a sufficient circulation can be maintained with a ventricular rate between 30 and 40, but render it doubtful whether at slower rates an efficient circulation is still possible.

Although the experiments on the subject were comparatively unsuccessful, the probable mechanism of the reaction of these cases to exertion is interesting. Two of the circulatory reserves, increase in heart rate and increase in stroke volume, are very definitely limited. In D.C. the maximum ventricular rate which was observed was 52 per minute during the pulsus bigeminus which occurred frequently in him after exertion. His S.V. at rest was 114 cc. and that of the other two about 150 cc. and the S.V. is unlikely to increase beyond 200 cc. Indeed it has been shown[60] that, from the size of the pericardium, 233 cc. must be about the maximum output possible for each ventricle. Taking a pulsus bigeminus of 52 as equal to 52 normal beats, c.f. digitalis bigeminy above, the maximum C.R. attainable in D.C. would appear to be 10.4 litres in place of the thirty or so litres attainable in a healthy individual. Yet the first two of these men got about fairly comfortably; another demonstration of the extent of the reserves nature provides.

CIRCULATION RATE IN CARDIAC FAILURE.

Those cases in this series showing signs of cardiac insufficiency in the resting state had, when the failure was so marked, without exception low circulation rates. (table 13). Of these the cases which improved showed with the improvement an increase in C.R. (Charts 1, 2 and 3). As has already been mentioned Meakins and Davies[41] also found the C.R. in cardiac failure to be low, and the actual C.Rs. in the cases reported by them correspond closely in magnitude with those in this series. When the C.Rs. in these cases are compared with those in the other patients with cardiac lesion who were examined, as has been done in table 14, it is found that the C.R. is definitely lower in them than in any of the others. In these cases also the stroke volumes (except in J.B. with complete heart block) are lower than in the others, and the oxygen utilization is higher. From these observations it would seem established that in definite cardiac failure the resting circulation rate is low.

Case.	H.R.	C.R.	S.V.	S.I.	A.V. O_2 diff.
Mrs D.	100	2.57	26	.46	13.64
Mrs S.	200	3.6	18	.51	7.82
J.H.	149	3.05	20.5	.28	8.34
J.D.	98	2.4	25	.65	8.43
J.B.	21	3.2	151	2.03	7.78

TABLE 13. Cardiac Failure.

The circulation rate is the product of the rate of the heart and of its output per beat, and it is evident that the low C.R. in all but one of these cases of cardiac failure above mentioned, is due to a deficient output per beat. The heart rate in these cases is rapid, possibly an attempt to compensate for the small S.V. It has already been shown that valvular lesions play little direct part in reducing the S.V. and it would seem that the small S.V.s and consequent low C.Rs. must be due chiefly to myocardial failure. In the cases of auricular fibrillation there is, of course, in addition to the incapacity of the myocardium to expel a sufficient amount of blood at each beat, the further handicap of the rapid irregular rhythm.

A contrast to these cases is presented in J.B. who had complete heart block. In him also there was a low C.R. associated with definite clinical signs of cardiac insufficiency, but his S.V. was large - 151 cc. - the low C.R. being due to the extraordinarily slow ventricular rate. This however cannot be a common mechanism in the production of the low circulation rate in cardiac failure.

If it be granted that the first four cases in table 13, in conjunction with those of Meakins and Davies, are representative of the more common types of cardiac insufficiency then it can be stated that in/

in cardiac failure of the ordinary type the low circulation rate is due to a failure of the myocardium to maintain a sufficient output per beat, rapid irregular tachycardia being a possible contributory factor in cases with auricular fibrillation. The deficiency of the cardiac output is not due, at least directly, to any valvular lesion which may exist.

In these cases as a result of the low C.R. there is an increase in the oxygen utilization (table 13). Here the Art. Ven O_2 difference is not directly measured but calculated from the C.R. and the Oxygen consumption. In Meakins and Davies cases the CO_2 Ven. Art. difference was measured, and was found to be increased in failure, while as already noted Lundsgaard[42] and Harrop[43] found an increase in the oxygen utilization in the blood passing through an arm in "decompensated" cardiac patients. This increase in the oxygen utilization is obviously a compensatory phenomenon, the third of the circulatory reserves being called into action on account of the failure of the other two, heart rate and stroke volume, to maintain a sufficient rate of blood flow.

It is to be expected that in cases of less advanced cardiac failure, lesser degrees of these changes, compensatory or otherwise, will still be evident, - a slightly low C.R. with a compensatory increase/

TABLE 14. A comparison between C.R., S.V. and oxygen utilization and the severity of failure as judged clinically. S.V. and H.R. are also compared.

Case	C.R.	Signs of Failure.	Case	S.V.	H.R.	Signs of Failure.	Case	Art. Ven. O_2 Diff.	Signs of Failure.
J.D.	2.4	+ + + +	Mrs S.	18	200	+ + + +	Mrs D.	13.64	+ + + +
Mrs D.	2.6	+ + + +	J.H.	21	149	+ + + +	J.D.	8.43	+ + + +
J.M.	3.05	+ + + +	J.D.	25	98	+ + + +	J.H.	8.34	+ + + +
J.B.	3.2	+ + +	Mrs D.	26	100	+ + + +	Mrs S.	7.82	+ + + +
Mrs S.	3.6	+ + + +	J.H.	49	96	+ +	J.B.	7.78	+ + +
D.C.	4.3	+	T. McN.	51	100	+ +	D.C.	6.07	+
J.H.	4.7	+ +	Mrs T.	52	105	-	R.N.	5.22	-
K.G.	5.0	+	K.G.	55	91	+	J.H.	5.77	+ +
T. McN.	5.1	+ +	E.B.	56	98	+	T. McN.	5.76	+ +
R.N.	5.2	-	R.N.	66	79	-	K.G.	5.17	+
Mrs T.	5.4	-	F.K.	88	81	+	G.S.	5.04	+
E.B.	5.5	+	Mrs F.D	91	76	+	Mrs T.	4.66	-
G.J.	5.5	+	W.R.	114	69	+ +	Mrs F.D.	4.33	+
Mrs F.D.	6.9	+	D.C.	114	37	+	E.B.	4.16	+
F.K.	7	+	J.B.	151	21	+ + +	F.K.	3.4	+
W.R.	7.9	+ +	G.J.	154	36	-	W.R.	2.85	+ +

increase in oxygen utilization or possibly merely an increase in heart rate which compensates for a deficient S.V. Table 14 was drawn up in an endeavour to obtain definite information on this point. In it, the results from all the cardiac patients being included, C.Rs. and S.Vs. have been arranged in ascending order of magnitude and oxygen utilization in the reverse order with opposite each a rough indication of the extent of cardiac failure as judged clinically. Examination of this will show that, even apart from the extreme cases of failure, there is a distinct tendency for those cases with the most evidence of failure to appear high in the columns, i.e. to have a relatively low C.R. and S.V. and a high oxygen utilization. Those cases having the lowest S.V.s also tend to have the most rapid heart rates. The only notable exception to this, apart from the high S.V. in the case of heart block who had definite failure, is W.R. This man became breathless on even moderate exertion, although he had a C.R. of 7.9 L, S.V. 116 cc., H.R. 69 and oxygen utilization of 2.85 vol. %; but in him, as has been before noted, there was the complication of a definite but undetermined degree of anaemia. The information to be drawn from this table is at least not antagonistic to the hypothesis put forward, but is quite insufficient to prove it correct. Indeed before any definite conclusions could/

could be reached as to the significance of such circulatory changes, much more would require to be known about the possible variations which might occur in the healthy individual. It seems logical however to assume, unless and until it be definitely proved otherwise, that the same circulatory changes, though to a lesser degree, occur in early and in late cardiac failure.

Since in cardiac insufficiency the circulatory reserves are being called upon even in the resting state, obviously the extent to which the oxygen consumption can be increased will be limited, and consequently the capacity for exertion will also be limited. As a result the usual early indication of circulatory insufficiency - dyspnoea - will develop, not, as in the normal person only on severe exertion, but on slight exertion, or as the process proceeds will be manifest even with the patient resting.

With a low C.R. stagnation of the blood in the peripheral vessels is to be expected; indeed, increased stasis in the capillaries of the nail fold in cases of auricular fibrillation during periods of failure has been demonstrated cinematographically[61]. With this stasis there will be an increased amount of oxygen absorbed from the blood by the tissues - the increased oxygen utilization above noted - . As a result the blood of the capillaries and small venules will be of a darker colour than usual, and

if/

if this is marked, cyanosis will result. Where there are no pulmonary complications - hydrothorax, hypostatic congestion etc, - definitely obstructing the absorption of oxygen from the lungs, this would appear a likely explanation of the cyanosis occurring in cardiac failure.

The stasis due to the low C.R. and the malnutrition of the capillary walls resultant therefrom, would also explain the oedema of cardiac failure, occurring as it does in the most dependent parts where stasis will be most marked.

The fact that signs of circulatory stasis - oedema or chronic venous congestion - may occur in one case only in the pulmonary circulation, in another only in the systemic, has been brought forward recently by German workers[62] as an argument against cardiac insufficiency being due to a low C.R., as to the occurrence of which they profess doubt. They appear inclined to attribute the insufficiency to a "failure of ventricular balance". It was shown by Starling[9] (p.p. 12) that in the heart lung preparation either of the ventricles might show fatigue (failure) before the other. If the left ventricle first became fatigued, there was a gradual rise in pulmonary venous pressure, resulting in the increased filling of the left ventricle now necessary to maintain its output. Similarly if the right ventricle first became fatigued, the systemic venous pressure rose and the right ventricle dilated. This increased venous pressure in

one/

one or other of the circulations entails a relative increase in the amount of blood in the venous side of that circulation and consequently, since the rate of flow in the two circulations must of a necessity remain the same, entails also increased stasis there. How this in the absence of a low C.R. will explain all the phenomena of cardiac failure is not clear. It does, however, offer an explanation of the fact that in cardiac failure the signs of stasis may be limited to or most marked in either the systemic or the pulmonary circulations.

From a consideration of these points it would appear that the low C.R. is not a mere occurrence in cardiac failure but the primary factor on the basis of which the various other phenomena occurring can be explained.

It will be recalled that in the maintenance of the oxygen supply to the tissues, three factors are concerned, heart rate, stroke volume, and oxygen utilization, and that each of these is a potential reserve which may be called upon if the demand for oxygen increases. The first two of these functions are concerned solely with the maintenance of the circulation rate, and in such cases as have been considered, one or other of them, much more usually the stroke volume, has been reduced by the pathological process/

process from which the patient suffers, to a level far below that found in the normal resting individual. As a result the two remaining reserves, probably also to some extent limited, are called upon even during the resting state. As the stroke volume continues to decrease, these reserves are called upon increasingly, and eventually a time comes when they are being called upon to a maximum even at rest. This is analogous to the increasing call on the circulatory reserves occurring in continued severe exertion. Thus the resemblance of the symptoms of cardiac failure due to disease to those of circulatory distress in the normal person after severe exercise, which was always insisted upon so strongly by Sir James McKenzie.

THE EFFECT OF DIGITALIS ON THE CIRCULATION RATE.

In seven of the cardiac patients opportunity was taken to study the effect of digitalis on the C.R. The digitalis was given as the powdered leaf by the massive dose method according to the formula of Eggleston (.015 G. Pulv. Dig. Fol. per pound body weight). The dose was fractioned into three or sometimes more parts, and given over a period usually of 12 or 24 hours.

After and sometimes during the administration of many of the doses there was more or less marked nausea and vomiting. This occasionally occurred almost immediately after a fraction had been taken, usually the second or third, occasionally the first, being in many of these cases apparently either of psychic origin or due to a local irritant action of the digitalis. In other instances nausea or vomiting did not commence until some time after the last fraction had been given, or grew more pronounced then. This was the true toxic vomiting and was usually more severe and longer lasting than the other type. In either case there is a possibility of the full therapeutic digitalis effect on the C.R. being masked because of loss of digitalis or because the exertion of vomiting or the increased vagal tone resultant or nausea/

Case.	Before Digitalis.			After Digitalis.			% Change.		
	H.R.	C.R.	S.V.	H.R.	C.R.	S.V.	H.R.	C.R.	S.V.
Mrs D.	100	2.57	26	70.3	3.17	45	-29.7	+23	+73
	93	2.88	31	72.3	3.57	49	-22	+24	+58
	91	3.33	36.3	62	5.1	83	-32	+53	+128
	80.7	5.37	67	74.3	3.8	51.3	-8	-29	-23
	80	4.75	59.5	79.5	7.1	90.5	-1	+49	+52
Mrs S.	200	3.6	18.3	104	6.47	65.3	-48	+80	+257
*	107	5.25	49	97	4.75 *	48.5	-9	-10	-1
J.H.	96	4.7	49	91	4.4	49.5	-5	-6	+1
	149	3.05	20.5	82	4.2	51	-45	+38	+149
J.D.	98	2.43	24.7	83	2.45	29.5	-15	+1	+19
Mrs T.	105	5.37	51.7	68.3	4.1	60.3	-35	-24	+17
T. McN.	100.3	5.13	51.3	89.3	5.03	56.3	-11	-2	+11
K.G. *	92	4.9	53	81	6.0	74	-12	+22	+40

TABLE 15. Effect of Digitalis on Cardiac Output.

* Averages thus marked are of doubtful value.

nausea was affecting the C.R. at the time of a determination. A few observations only appear to have been affected by these or other extraneous factors, and those have already been mentioned in the preliminary observations on the results.

In glancing over the results from those patients who received digitalis, it is immediately obvious that in the first three, who had definite cardiac failure, many of the doses of digitalis have been followed by a more or less marked rise in C.R. while in the other patients there does not appear to have been any such result. The rise in C.R. after the doses of digitalis is very well shown in the charts from the first three cases. In the second two, Mrs S. and J.H., it is noticeable that while the doses given during periods of definite cardiac failure have apparently produced dramatic changes in the levels of H.R., C.R., and S.V., those given when a more efficient circulation was being maintained are without any such marked effect.

In order that the effects of the digitalis might be more easily studied table 15, in which the average H.R., C.R. and S.V. before and for one week after the various doses of digitalis are given and compared, has been prepared. Out of the fifteen doses given sufficient determinations have been done bearing on eleven, to render these averages reliable. In two other instances the determinations are insufficient in numbers and the averages are of little value.

Before/

Before one dose no preliminary observations were done and it has been omitted from consideration, while the last dose given to Mrs D. has, for reasons already stated, also not been considered.

Of the eleven doses on the effect of which reliable information was obtained, six caused a definite increase in C.R., three did not appreciably affect it, and two apparently decreased it. The six doses which caused an increase were given to the first three patients, four to Mrs D. and one each to Mrs S. and J.H. Mrs D. before the first three of these doses had a low C.R. and quite definite signs of cardiac insufficiency. When the other dose which caused an increase was given, the C.R. was being maintained at a higher level and signs of insufficiency though still present, were not so marked. The doses causing an increase in Mrs S. and J.H. were both given in the presence of a low C.R. and very definite cardiac failure. Two of the doses producing no effect on the C.R. were given while the patients (one of whom was J.H.) had no very definite signs of cardiac failure and a moderate circulation rate. In the other (J.D.) the C.R. was low and the insufficiency definite, and the digitalis besides not increasing the C.R. produced no improvement in the patient's condition. One of the doses apparently causing a decrease in C.R. was given to Mrs D. and it has already been pointed/

pointed out that it is very doubtful whether the digitalis had anything to do with the diminution in blood flow (p.p. 73). The other was given to Mrs T., a case of auricular fibrillation with no symptoms of cardiac insufficiency, whose C.R. was not low. The decrease after this dose appears to have been due to the drug.

The C.R. then may be increased, decreased or unaffected by digitalis, different effects occurring not only in different patients but also in the same patient at different times. An increase appears most likely to occur where there are signs of cardiac insufficiency and a low C.R., but in such cases does not invariably occur. When signs of cardiac failure are either little marked or absent, and the C.R. is not definitely low, an increase seems unlikely, the C.R. usually remaining unaltered or diminishing.

The heart rate after these doses of digitalis has in most instances been diminished, in a few has remained practically unaffected, and has increased in none. Conversely the S.V. has either been increased or has remained unaffected after each dose except one. This one dose after which the stroke volume apparently decreased was that given to Mrs D., about the effect of which doubt has already been expressed.

It is conceivable that of these changes in H.R. and S.V. one alone might be caused directly by the digitalis, the other being a compensatory phenomenon. Thus/

Thus if the heart rate were slowed by the drug the S.V. owing to increased diastolic filling might increase and the C.R. be maintained. Paradoxical as it may seem, decrease in the heart rate might even increase the C.R. In Mrs S. for instance it has already been shown that the low C.R. existing before digitalis was given was partly due to the rapid ventricular rate. On the other hand digitalis may primarily increase the contractile power of the myocardium and consequently the S.V. The heart rate, if previously accelerated in an endeavour to maintain the C.R., would then fall, the need for acceleration having been removed. But it is difficult to see how digitalis could in that way lower the C.R. Obviously neither of these hypotheses is sufficient to explain every case. Digitalis must have two separate actions:- (1) to slow the heart rate (2) to increase the output per beat. Doubtless, however, in some cases a certain amount of compensatory change may occur in either H.R. or S.V.

In most cases these two actions of digitalis must, as far as the effect on the C.R. goes, be antagonistic and this in itself is an explanation of the inconstancy of the effect of digitalis on the C.R. (cf. Cushny's conclusions given on p.p. 53).

Where there is definite cardiac failure and the circulation rate and stroke volume are low, the increase in/

in S.V. resultant on digitalis may be such that, notwithstanding any pulse slowing which may occur, the C.R. is increased. This has occurred in each of the cases of cardiac failure in which the effect of digitalis was observed, with the exception of J.D. She showed no increase in C.R. after digitalis, nor was there any increase in S.V. which could be attributed to the drug, the apparent 17% increase which happened to occur being due to the low initial stroke volumes, the heart rate having been quickened by excitement during these determinations. The myocardial damage in this patient was very marked, so much so probably that the muscle was unable to respond to the digitalis. Where there is no definite cardiac failure and the C.R. and S.V. are not low, the increase in S.V. after digitalis, if any occurs, is small. In these cases the C.R. remains unchanged unless, as in Mrs T., the slowing in heart rate is such that the output per minute is actually lessened.

Digitalis then may increase the contractile power of a weakened myocardium, but does not appear further to strengthen an efficiently acting myocardium. There is no evidence in the cases examined that digitalis, in therapeutic doses, can diminish the stroke volume.

Cases of auricular fibrillation with a rapidly acting heart have long been known to respond especially favourably to digitalis, and the two cases here observed/

observed were no exception. The explanation would appear to be that the slowing of the heart rate in these cases actually increases the circulation rate, since the rapid irregular rhythm in itself reduces the cardiac output, whereas in cases with normal rhythm, slowing the heart rate decreases the circulation rate. In other words, in auricular fibrillation the two actions of digitalis augment one another, while in normal rhythm they are antagonistic.

A further point of especial clinical interest is, that apparently a definite increase in C.R. can occur without the heart rate being appreciably altered. After one of the doses given to Mrs D. there was an increase of 49% in C.R. with practically no alteration in heart rate.

As to the action of digitalis being what it is the method by which it produces improvement in cases of cardiac failure is obvious. It raises the low circulation rate to which all the signs and symptoms of the failure are due. This, the obvious explanation of the improvement resulting from digitalis in cardiac failure, has from time to time had doubt thrown upon it by workers who have applied results obtained in healthy animals to disease in man.

A N A E M I A.

In cases of anaemia there is a possible fallacy in the circulation rate determination which cannot obtain to any extent in cases of other types. The figure used throughout these determinations for the coefficient of solubility of ethyl iodide in blood is 2. This figure was determined by Henderson and Haggard[1] using blood with 100% Hb. and it would seem possible that a reduction of the Hb. content of blood might also reduce its capacity for absorbing ethyl iodide. From the work of Henderson and Haggard[1] this would not appear likely, for they found the coefficient of solubility of ethyl iodide in water also to be approximately 2. Starr and Gamble[54] on the other hand, in their paper criticising the ethyl iodide method, state that while the coefficient of solubility of ethyl iodide in blood containing 100% Hb. is, according to their method of analysis, 7.6, in anaemic blood it may be as low as 2. Like their main thesis, the validity of this observation depends on the accuracy of their method of analysis and this cannot be accepted as proved. It has therefore been assumed that in anaemic as in normal blood 2 is a sufficiently close approximation to the coefficient of solubility of ethyl iodide for the purposes of the circulation/

circulation rate calculation.

In the three cases of anaemia which were investigated, the determinations at the beginning of the series were made with the patients either in bed or lying on a trolly in which they had been wheeled from their beds. Later when they were more convalescent the determinations were made with the patients lying on a couch after 30 minutes rest. The sudden change in the C.R. in Mrs K. from a level between 6.5 and 7.5 litres to between 9 and 10 litres which commenced with the determination made on the 9th April does not appear to be due to this change in the experimental conditions. The two previous determinations had been made with the patient on the couch, and in them the C.R. was still at its old level while later two of the determinations were made purposely with the patient in bed but the C.R. still remained high. Apart from this, which is a change entirely the reverse of what was expected, the C.R. in the first two patients remains more or less on the same level notwithstanding an increase in Hb. from 20% to 60% in the first and to 50% in the second. In both these cases the initial C.R. is high, but no higher than might occur in normal individuals at rest.

The third patient, M.S., differed from the others in that his anaemia was of the pernicious type. In his case the improvement in Hb. content which occurred with/

with treatment appears to be associated with a definite fall in C.R. The last two determinations on this patient were made after his discharge from the ward on occasions on which he reported as an outpatient and, although he had the same period of rest before the determinations, the C.Rs. are decidedly higher than those previously determined at the same Hb. content. The C.R. in this patient was at its highest only 6.2 L., and with the Hb. at 70% fell as low as 3.9 L. This comparatively low C.R. level is probably due to myocardial deficiency - there was besides dyspnoea on exertion well marked oedema of the feet and legs, especially in the evening when the patient was up and about.

The Hb. estimations in these cases were done with a Haldane haemoglobinometer usually, but not always on the same day as the C.R. determination.

Mrs K. Age 32. Wt. 57.2 - 65.8 Kg. Secondary Anaemia.

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume Litres per min.	Alv. CO_2.	Oxygen Consumpt. c.c. per min.	Art. Ven. O_2 diff. Vols. per cent.	Hb.%	Remarks.
8.2.27	78	7.2	93	1.63	6.85	-	248	3.44	20%	
10.2.27	76	6.8	89	1.56	6.15	4.68%	236	3.47	26%	
16.2.27	76	7.5	99	1.73	5.97	4.28%	264	3.52	30%	
24.2.27	71	7.1	101	1.68	5.46	4.52%	233	3.28	36%	
3.3.27	67	7.1	106	1.77	5.19	4.78%	249	3.51	40%	
23.3.27	78	6.5	84	1.40	6.15	5.08%	286	4.40	40%	Rested 30 mins on co
26.3.27	72	7.2	100	1.67	5.3	5.47%	257	3.57	-	" " "
9.4.27	77	10.1	130	2.05	6.37	-	245	2.43	46%	On couch.
15.4.27	75	10.9	126	1.99	6.58	5.35%	256	2.35	46%	In bed. Noisy valve
23.4.27	66	9.2	139	2.19	5.60	5.25%	244	2.65	54%	On couch.
27.4.27	68	9.7	143	2.25	5.39	5.23%	243	2.51	56%	" "
11.5.27	68	8.9	131	1.99	5.67	5.17%	247	2.78	60%	In bed.
J.L. Male. Age 24. Wt. 51 Kg. Secondary Anaemia.										
4.3.27	89	7.7	86	1.57	7.1	4.69%	327	4.24	20%	On trolly.
17.3.27	79	7.3	92	1.80	7.41	4.79%	-	-	30%	On couch. 30 mins. re
31.3.27	67	6.2	93	1.82	5.79	5.18%	255	4.11	40%	" " " "
9.4.27	89	7.0	79	1.55	6.62	5.21%	264	3.77	36%	" " " "

J.L. (contd.)

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume Litres per min.	Alv. CO_2.	Oxygen Consumpt. c.c. per min.	Art. Ven. O_2 diff. Vols. per cent.	Hb.%	Remarks.
21.4.27	68	7.6	111	2.17	6.35	5.46%	260	3.42	50%	On couch 30 min. rest.
30.4.27	77	6.5	85	1.67	6.20	5.22%	280	4.31	46%	" " "
4.5.27	73	7.4	101	1.98	6.74	5.5%	291	3.93	-	" " "
M.S. Male. Age 66. Wt. 55.5 Kg.							Pernicious Anaemia.			
15.2.27	70	6.2	88	1.59	9.47	4.34%	-	-	38%	On trolley.
21.2.27	73	6.4	88	1.59	9.28	-	216	3.38	45%	" "
26.2.27	66	5.4	82	1.48	9.29	4.0%	295	5.46	54%	" " dozing.
4.3.27	58	5.2	90	1.62	6.46	4.87%	238	4.58	64%	On couch.
16.3.27	68	3.9	58	1.05	8.13	-	-	-	60%	On couch.
6.4.27	61	4.0	65	1.17	6.65	5.27%	220	5.5	70%	" "
22.4.27	71	5.5	77	1.39	7.94	5.28%	276	5.0	70%	Out patient. On couch.
13.5.27	67	5.0	75	1.35	8.53	5.17%	298	5.96	64%	" " " "

CASE HISTORIES.

Mrs K.

Age 32. Housewife. One child aged 5.

"Bloodless" since aged 18-20. Headaches, breathlessness, palpitation and gastric disturbance.

Anaemia of secondary type with very low colour index. Cause not ascertained.

Heart not enlarged. Haemic murmurs. Bruit de diable.

Treatment. High purin diet. Later (11.4.27) Pil. Ferri also.

Diagnosis. Secondary Anaemia.

J.L.

Male. Age 24. Clerk.

Marked anaemia of secondary type of apparently about three years duration. Causal factors not discovered.

Heart not enlarged. Haemic murmurs all areas. Bruit de diable.

Treatment. High purin diet. Later Pil. Ferri also.

Diagnosis. Secondary Anaemia.

M.S./

M.S.

Male. Age 66.

Progressive weakness, swelling of feet and ankles for 13 months. Yellowish tinge. Dark pigmented patches on buccal mucosa and skin of legs.

B.P. $\frac{100-120}{50-60}$.

Heart $\frac{11}{\frac{1}{2}/4''}$ in 5th L. space. No bruits, 1st mitral impure. Complete achlorhydria. No X-ray evidence of gastric carcinoma. W.R. - .

Colour index 1.1 to 1.3. Film suggestive of P.A.

Treatment. High purin diet.

Diagnosis. Pernicious Anaemia.

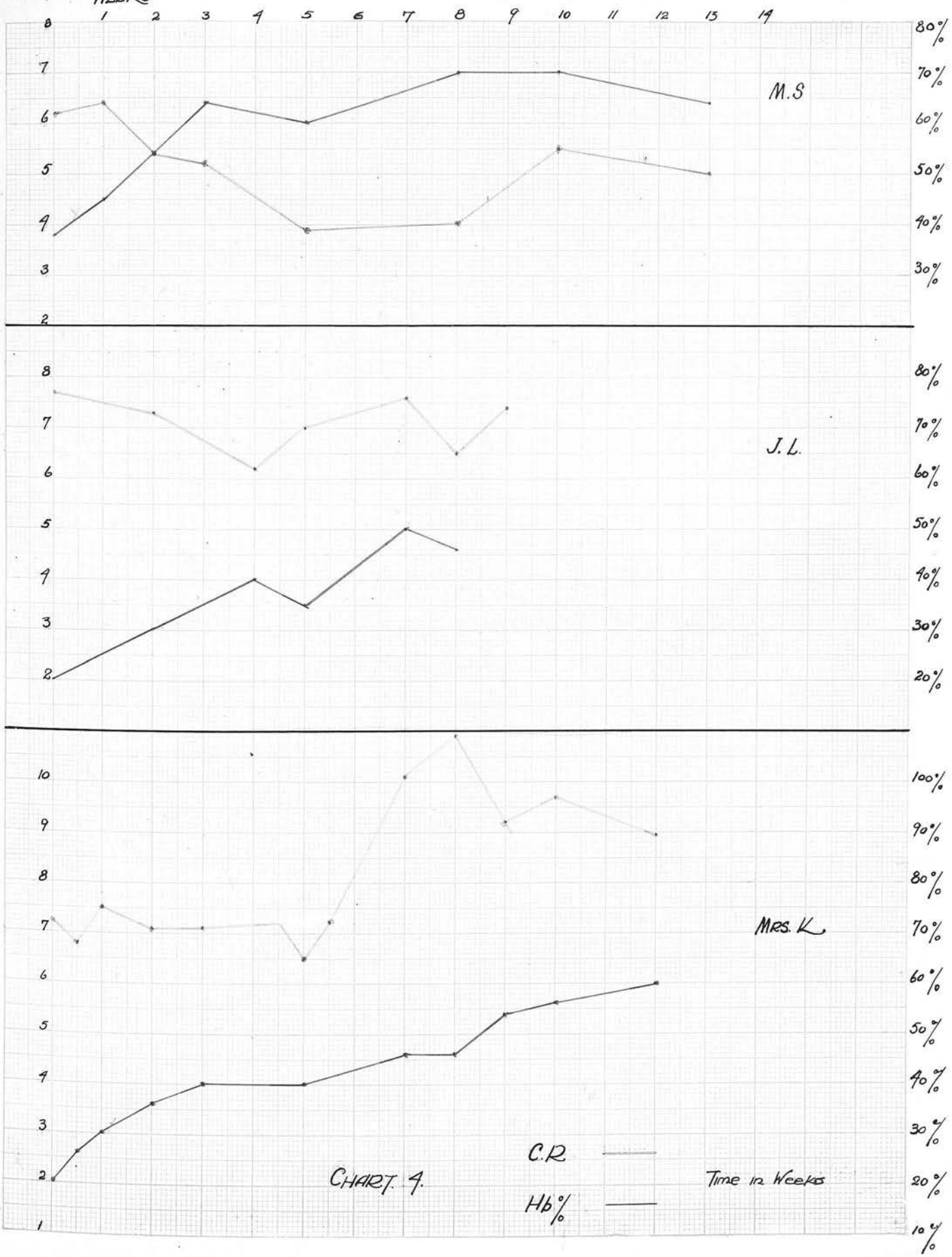

WEEKS
1 2 3 4 5 6 7 8 9 10 11 12 13 14
8 7 6 5 4 3 2
80% 70% 60% 50% 40% 30%
M.S
8 7 6 5 4 3 2
80% 70% 60% 50% 40% 30% 20%
J.L.
10 9 8 7 6 5 4 3 2 1
100% 90% 80% 70% 60% 50% 40% 30% 20% 10%
MRS. K
C.R
Hb%
Time in Weeks

CHART. 4.

D I S C U S S I O N.

Circulation Rate in Anaemia.

While discussing cardiac failure it was pointed out that the efficiency of the circulation depended on three factors, the pulse rate and the output of the heart per beat, which together maintain the circulation rate, and the oxygen utilization. The circulatory failure in cardiac insufficiency of the ordinary type was shown to be due primarily to the inability of the heart to maintain a sufficient output per beat, the heart rate and the oxygen utilization being increased in an endeavour to compensate for this. In anaemia, in which if it is severe signs of circulatory insufficiency also occur , obviously the factor which is primarily at fault is the oxygen utilization or rather the oxygen capacity of the arterial blood and any compensation necessary for this must be provided by increase in circulation rate.

The oxygenation of the blood in the lungs being unimpeded, the oxygen capacity of the arterial blood is proportional to the Hb. content, and in chart 4 the relative changes in the Hb. and the C.R. occurring in the three cases of anaemia observed are given. The initial value of the C.R. in these cases 7.2, 7.1, and 6.2 litres with Hb. contents of 20%, 20% and 38% are none of them higher than might be expected in/

in similar healthy individuals. In each case there is a steady and fairly extensive rise in the haemoglobin but in one only is there an accompanying fall in the C.R. such as one might expect if the C.R. had increased to compensate for the diminished oxygen capacity of the arterial blood when the haemoglobin was low. The diminution in C.R. in the case mentioned appears to be due to a decrease in S.V. rather than to a decrease in heart rate. In one of the others (J.L.) the C.R. kept at a fairly constant level between 6.2 and 7.5 litres per minute, while in Mrs K. the C.R. remained on a level between 6.5 and 7.5 litres for 7 weeks and then rose sharply to 10 litres and continued between 10.9 and 8.9 litres. This marked rise in the level of the C.R. was associated with no special change in the Hb. content which continued to increase gradually. It does not therefore seem attributable to any change in the capacity of the blood to absorb ethyl iodide, and it has been shown not to be due to change in the experimental technique.

With a Hb. content of 20% the oxygen content of fully saturated arterial blood would be 3.7 vols. %. In Mrs K. the Art. Venous O_2 difference as determined at the first circulatory experiment was 3.44 vol. %. This, if correct, means that 93% of the available oxygen was utilized. The oxygen utilization in this case remained more or less steady until it decreased sharply/

sharply with the increase in C.R. above noted. As the oxygen capacity of the arterial blood was at the same time increasing there is a diminution throughout the period of observation in the percentage utilization of oxygen.

In the first observation made on J.L. there is obviously somewhere an experimental error. The art. venous O_2 difference, as calculated from this circulatory experiment, is actually higher than the maximum possible oxygen content of the arterial blood. Whether the error lies in the Hb. estimation or in the determination of the C.R. or the oxygen absorption it has not been possible to determine. Apart from this first erroneous observation, the oxygen utilization remains fairly constant throughout the series, while the percentage utilization again rises slightly.

In M.S. in whom the C.R. decreases there is an increase in the oxygen utilization. The percentage utilization in this case remains about 40%.

Obviously the C.Rs. in the earlier parts of these series, at least in the first two, are minimal or almost so, i.e. they provide a flow of blood just sufficient to maintain the necessary oxygen supply to the tissues if all the oxygen is utilized. These results support the opinion of Lundsgaard that "the anaemic organism makes no circulatory response until the whole of the available oxygen has been utilized."

It must be remembered that in severe anaemias, and especially when they are of long duration, the myocardium will be damaged by persistent under-nutrition. This in itself will tend to reduce the C.R. and possibly explains the lack of response in such cases as those investigated. Blalock and Harrison[48] noted in their dogs that the highest C.Rs. were obtained not when the anaemia was most severe but later during recovery, i.e. when the myocardium was regaining power. In the same way the rise in C.R. in Mrs K., occurring after the Hb. had been increased for some considerable time, may have been due to an increase in the power of the myocardium resulting from better nutrition. Certainly the general condition of the patient had by then much improved.

Of a necessity any increase in the oxygen consumption occurring in such anaemic individuals must be met entirely by increase in circulation rate. Since the maximum C.R. possible, even in healthy individuals, appears to be not more than 30 litres, a three or at most four-fold increase in oxygen consumption is the utmost they can be capable of.

HYPERTHYROIDISM AND MYXOEDEMA.

The next five cases, three exophthalmic goitres and two myxoedemas, are grouped together, since in both these conditions the main point of interest in regard to the circulation rate is its relationship to the general metabolism.

All but a few of the determinations in these cases were done with the patients under basal conditions, after a fast of 12 hours. Where these conditions have not obtained, this is remarked on. In the first case, E.H., two determinations were made without the patient being under basal conditions and in circumstances which made her much more excited than did the manoeuvres at other times. The C.Rs. at these determinations were by far the highest noted in this patient, at least double the level of C.R. obtaining at the time. In Mrs McC. one of the myxoedemas, the first observations were also done without regard to basal conditions. These results do not show the extreme divergence from the general level of the two in E.H. though they tend to be higher than later C.Rs. determined at the same rate of metabolism. This would appear to indicate that the circulation rate reacts to excitement and other disturbing factors much more markedly in exophthalmic goitre than in myxoedema/

myxoedema - as would be expected.

The goitres were each treated by rest and iodine, either Lugol's solution or the 10% tincture in doses varying from minims V-XV t.i.d. In two during the period they were under observation a very definite fall in metabolism occurred and in these two, E.H. and A.S., the C.R. also fell. One of them, E.H., had a subtotal thyroidectomy done, but unfortunately the only observation possible after this had to be done in circumstances far from basal. Thus no information as to the effect of the procedure was obtained.

The other goitre did not improve during the short time she was under observation and both metabolism and C.R. remained fairly constant.

In Mrs McC. the myxoedema, 19 determinations were made over a period of three months and during this time there was an exceptional opportunity of studying the effect of variation in metabolism on the C.R. On thyroid on admission, the effect of this was allowed to pass off, and when a low level of metabolism was reached an intravenous dose of synthetic thyroxin was given, an immediate and very marked rise in metabolism resulting. This was associated with a marked increase in circulation rate, and in heart rate, with some irregularity in rhythm due to extra systoles. After the effect of the thyroxin had passed off, the same preparation was tried by the mouth with no noticeable effect/

effect, and thereafter the patient was put again on thyroid extract. Throughout the changes in H.R., C.R. and metabolism appear roughly to be parallel. A few observations were out of line, notably that on 12.2.27 which shows a rise in C.R. despite a falling H.R. and metabolism. As there is no direct evidence of experimental error or change in technique, this determination cannot be altogether discarded.

In Mrs S. no very marked change in metabolism, which throughout was low, occurred, nor did the C.R., also low, show any marked variation.

E.H. Age 16. Wt. 40.5 - 45.5 Kg. Female. Exophthalmic Goitre.

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume Litres per min.	Alv. CO_2	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols. per cent.	Remarks.
26.2.27	140	6.2	44	1.02	7.79	5.32%	402	.73	6.48	
28.2.27	112	5.1	45	1.05	7.60	4.33%	349	.72	6.84	
1.3.27	100	4.3	43	1.00	7.40	4.27%	304	.75	7.07	
9.3.27	112	9.7	86	2.00	9.15	4.97%	-	-	-	2.30 p.m. Not fasting. Excited.
18.3.27	72	4.3	59	1.29	5.93	4.77%	234	.79	5.44	
21.3.27	Operation. Subtotal Thyroidectomy.									
18.4.27	104	9.5	91	2.0	6.49	5.33%	339	.69	3.57	As outpatient. 1 hr. on couch. Not fasting. Excited.

A.S. Age 26. Female. Wt. 48.5 Kg. Exophthalmic Goitre.

30.3.27	110	9.0	82	1.69	8.75	4.96%	357	.83	3.96
5.4.27	82	8.2	98	2.0	5.11	4.84%	275	.74	3.35
11.4.27	80	8.2	102	2.08	5.19	5.29%	256	.82	3.12
15.4.27	78	6.2	80	1.45	5.15	5.29%	244	.72	3.94
25.4.27	91	6.8	75	1.63	4.77	5.29%	210	.88	3.09

Mrs W. Age 51. Wt. 44.5 Kg. Exophthalmic Goitre.

11.5.27	134	7.1	53	1.21	8.56	4.37%	331	.74	4.66
13.5.27	125	7.2	57	1.28	9.33	4.22%	370	.62	5.14
18.5.27	110	7.8	71	1.60	8.1	4.33%	371	.6	4.76

Mrs McC. Age 45. Wt. 80 - 70.8 Kg. Myxoedema.

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume Litres per min.	Alv. CO_2	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols. per cent.	Remarks.
31.1.27	84	6.2	74	.93	4.88	4.59%	177	.77	2.85	
1.2.27	83	4.5	54	.68	4.3	4.65%	137	.78	3.49	Not Fasting.
2.2.27	86	6.7	78	.98	4.52	4.59%	195	.75	2.90	
3.2.27	71	5.0	71	.89	4.47	4.36%	197	.73	3.94	
5.2.27	58	4.4	75	.94	4.46	3.85%	146	.75	3.32	
8.2.27	57	4.4	77	.96	4.43	-	171	.70	3.89	
12.2.27	50	5.4	108	1.35	4.14	4.27%	165	.70	3.06	
16.2.27	Thyroxine 10 mgm. I.V.									
18.2.27	90	5.6	63	.79	6.05	4.23%	269	.64	4.8	
19.2.27	81	6.8	84	1.05	5.17	4.42%	227	.75	3.34	
21.2.27	77	6.8	88	1.10	5.89	4.60%	253	.64	3.72	Occasional Extra-systoles.
24.2.27	77	5.0	66	.83	5.97	4.42%	251	.65	5.02	
26.2.27	79	5.1	64	.80	5.85	4.26%	257	.69	5.04	
7.3.27	65	5.6	86	1.01	5.32	4.31%	227	.74	4.05	
21.3.27	57	4.6	81	1.13	5.16	4.50%	-	-	-	
1.4.27	50	4.6	93	1.31	5.12	4.04%	167	.91	3.63	28.3.27 Thyroxin 10 mgm. by mouth.
8.4.27	49	4.6	95	1.30	4.80	4.67%	174	.93	3.78	

15.4.27/

Mrs McC. (continued).

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per milo.	Resp. Volume Litres per min.	Alv. CO_2	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols. per cent.	Remarks.
15.4.27	56	5.2	85	1.30	5.45	4.39%	227	1.0	4.37	13.4.27. Ext. Thyr. Sicc. grs III t.i.d
26.4.27	87	5.8	67	.92	6.50	4.83%	249	.89	4.27	
6.5.27	81	6.4	79	1.10	6.48	4.52%	278	.74	4.34	
		Mrs Su.	Age 61.	Wt. 68 Kg.			Myxoedema.			
18.3.27	57	3.7	64	.94	4.18	4.84%	160	.76	4.32	
23.3.27	54	4.1	76	1.12	3.34	3.96%	143	.69	3.49	22.3.26. Thyroxin 10 mgm. by mouth.
1.4.27	50	3.0	60	.88	3.99	4.69%	152	.79	5.06	
8.4.27	61	3.5	58	.85	5.03	4.54%	144	.96	4.11	6.4.26. Thyroxin 30 mgm. by mouth.
12.4.27	58	3.1	54	.79	5.18	4.89%	190	.86	6.13	
26.4.27	69	3.7	54	.79	6.75	4.63%	184	.89	4.97	22.4.27. Ext. Thyr. Sicc. grs III. t.i.d.

CASE HISTORIES.

E.H.

Female. Age 16. Between-maid.

Nervousness, loss of weight and amenorrhea for 8 months.

Goitre and exophthalmus noticed for 2 months only.

Moderate uniform enlargement of thyroid, pulsatile, systolic bruit.

Pulse regular.

Heart not enlarged. Systolic murmurs all areas.

Marked degree of hyperthyroidism on admission, settled down quickly with rest in bed and Lugol's Iodine min. X. t.i.d. Transferred for operation.

B.M.R. + 74% → + 19%.

Diagnosis. Exophthalmic Goitre.

A.S.

Female. Age 26. Single.

"Nerves", goitre and slight exophthalmus for one year. Moderate uniform enlargement of thyroid with a systolic bruit over it.

Heart not enlarged. Systolic murmurs all areas.

On admission mild but definite hyperthyroidism. Settled quickly with rest in bed and Lugol's Iodine min. V. t.i.d.

B.M.R. + 37% → + 12%.

Diagnosis. Exophthalmic Goitre.

Mrs W.

Age 51. Housewife.

Admitted 9.5.27. Goitre and hyperthyroid symptoms noted for 9 weeks before admission.

Moderate uniform enlargement of thyroid. Usual eye signs present, also exophthalmos.

Heart $\frac{11}{1" / 4\frac{1}{2}"}$ in 6th space. Systolic bruit all areas. Rhythm regular.

Rest in bed. Lugol's iodine. Little improvement.

B.M.R. + 65% on 13.5.27.

Diagnosis. Exophthalmic Goitre.

Mrs M. McC.

Age 45. Housewife. 8 children.

Transferred from surgical ward after operation for ventral hernia. (stitch abscess during first few days in ward). Obvious Myxoedema.

Heart not enlarged. Blowing systolic murmurs all areas.

Treatment. Thyroxin intravenously and by mouth.

Ext. Thyroid Sicc.

B.M.R. - 40 → + 22%.

Diagnosis. Myxoedema.

Mrs Su.

Age 61. Housewife. 14 children. 5 misc.

Typical major myxoedema. In hospital on various occasions during past 4 years.

Heart/

Heart not enlarged; no murmurs; mitral first sound faint.

Treated on this occasion with thyroxin by mouth and later with Ext. Thyroid Sicc.

B.M.R. - 44% → - 11%.

Diagnosis. Myxoedema.

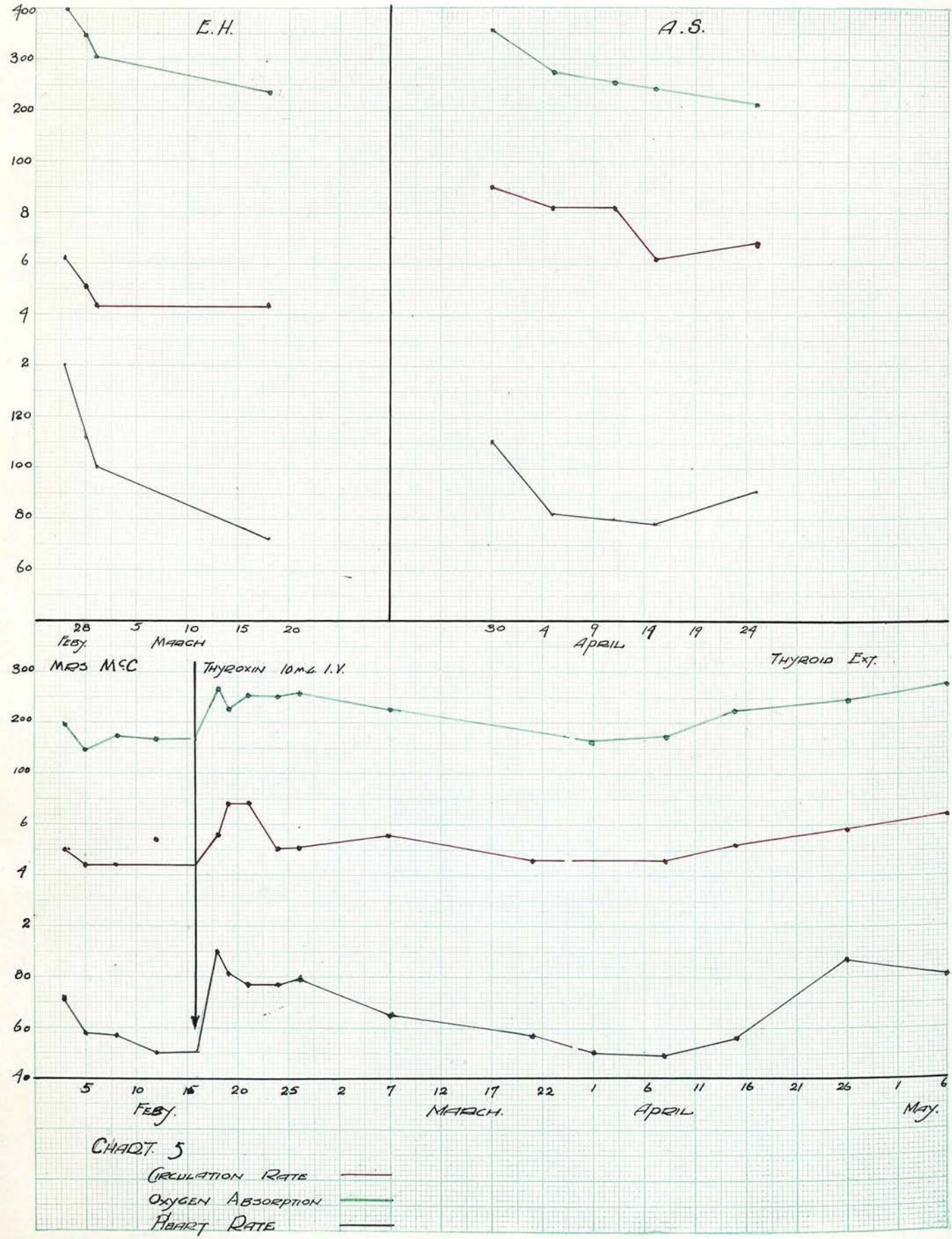
D I S C U S S I O N.

The Circulation in Hyperthyroidism and Myxoedema.

The problem in these conditions differs from that presented by those already considered in that, instead of a deficiency in some part of the circulatory mechanism, there is, by the alteration in metabolism, a change made in the demands of the organism on that mechanism.

In hyperthyroidism it is to be expected that provision will be made by the circulation for the increase in resting metabolism either by an increase in circulation rate or an increase in oxygen utilization or both. As the metabolism decreases so will the circulation return to normal. Similarly in myxoedema with the lessened demand for oxygen a decrease in C.R. or in oxygen utilization would be expected.

Of the goitres, while their metabolism was at its highest, one, A.S. had a C.R. of 9 litres and an oxygen utilization of 3.96 vol.%; in her obviously the increase in metabolism was provided for entirely by increase in circulation rate. In Mrs W., C.R. and oxygen utilisation - 7.1 litres and 4.66 vol.%, - while not outside normal limits, both tended to be high as if here C.R. and oxygen utilization shared the/


E.H.
A.S.
400
300
200
100
8
6
4
2
120
100
80
60
28 5 10 15 20
FEBY. MARCH
30 4 9 19 19 24
APRIL
MRS McC
THYROXIN 10 m.g. I.V.
THYROID EXT.
300
200
100
6
4
2
80
60
40
5 10 15 20 25 2 7 12 17 22 1 6 11 16 21 26 1 6
FEBY. MARCH. APRIL MAY.
CHART 5
CIRCULATION RATE
OXYGEN ABSORPTION
HEART RATE

the burden. In E.H. on the other hand the C.R. - 6.2 litres - is definitely not high while the oxygen utilization is. Yet as the metabolism decreases in this case it is the C.R. not the oxygen utilization which shows the most marked fall. As has been before noted, various other workers have found the C.R. to be high in exophthalmic goitre.

The myxoedemas both had a low C.R. and a more or less ordinary oxygen utilization. In Mrs Su. the C.R. is especially low, between 3 and 4 litres for the most part. The low C.R. in these cases, unlike that in cardiac failure, is sufficient for the body's needs and is not therefore associated with signs of circulatory insufficiency.

In three of the cases considerable changes in metabolic rate occurred while they were under observation, and in these cases there appears to be some degree of parallelism between circulation rate, heart rate and metabolic rate (Chart 5). In Mrs McC. a sufficient number of determinations were done to admit of this question being more thoroughly investigated. The coefficient of correlation between the oxygen absorption and circulation rate over the series of determinations done on this patient is $0.66 \pm .098$, indicating a definite though by no means complete correlation between these two factors. The extent

of/

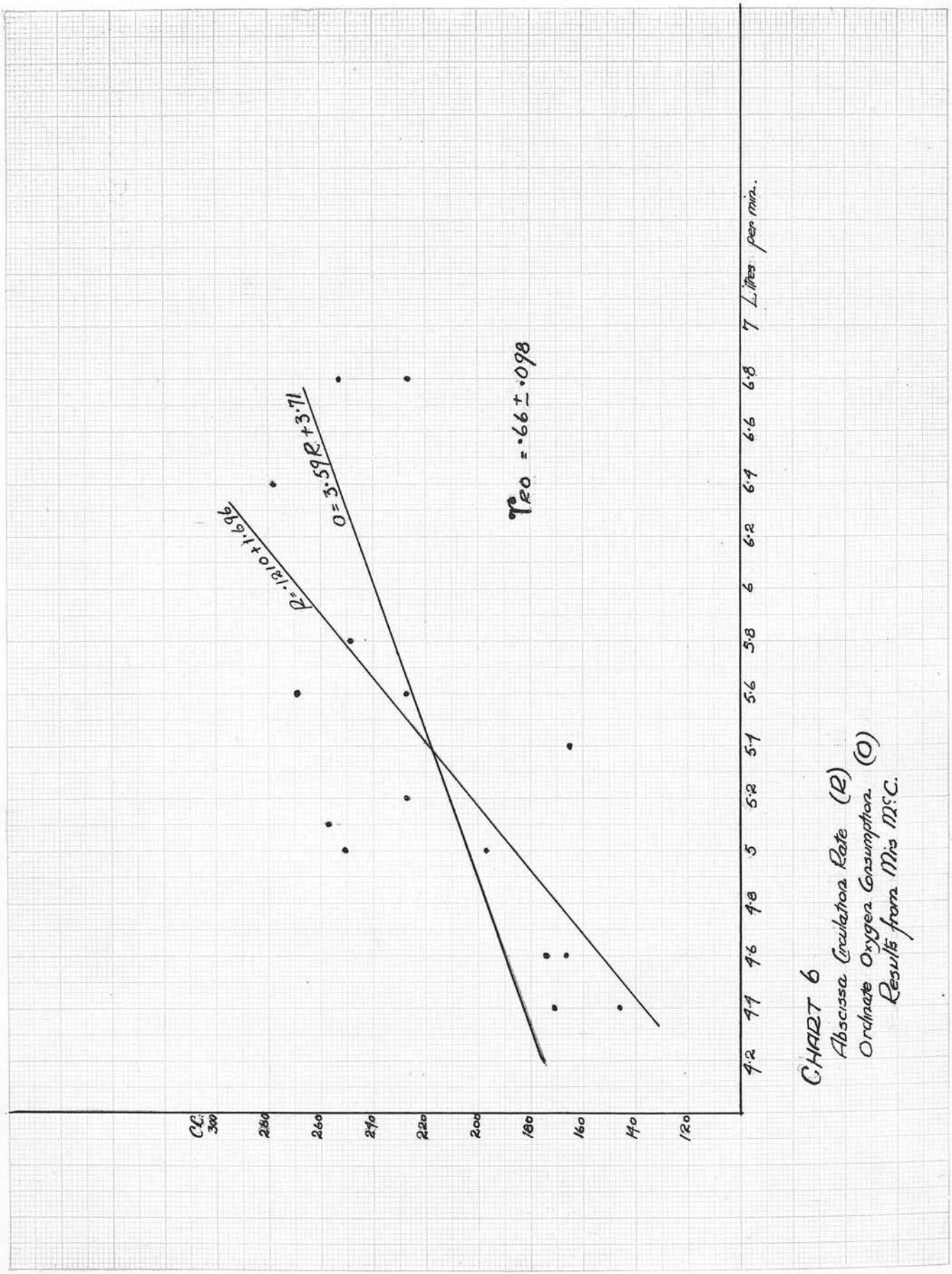


CHART 6
Abscissa Circulation Rate (R)
Ordinate Oxygen Consumption (O)
Results from Mis M.C.

of this correlation is also shown graphically in Chart 6. Were the correlation complete the two lines would coincide. That the correlation is incomplete suggests that the third variable, oxygen utilization, is also playing a part in meeting the changing demands on the circulation. In this connexion it is interesting to recall that Douglas and Haldane[20] found that during exertion the increasing circulation rate is not, on account of the changing oxygen utilization, absolutely proportional to the increase in metabolism.

Apparently then the varying demands on the circulation made by the changes in metabolism in these cases are met by changes in both circulation rate and oxygen utilization. That the changes in circulation rate are the more marked, is exemplified by the fact that the circulation rate is unusually high in exophthalmic goitre and low in myxoedema; while in individual cases of either condition a degree of parallelism exists between it and oxygen consumption.

That these changes in C.R. are to a great extent the result of changes in heart rate is obvious. Indeed in the cases here examined variation in S.V. appears to play little or no part in altering the C.R., nor does the S.V. show any definite tendency to vary with changes in metabolism.

This is in agreement with the results of Liljestrand and Stenstrom[51] in whose cases there

was/

was no evidence of change in stroke volume. On the other hand Meakin and Davies[50] found in their cases of exophthalmic goitre a definite reduction in stroke volume after operation suggesting that in these cases increase in S.V. had played a part in increasing the circulation rate.

MISCELLANEOUS CASES.

Of the two cases in this group the first was a girl with a moderate pleural effusion. The point of interest here was whether or not the removal of some of this fluid would affect the cardiac output. Before tapping the chest there is a steady fall in circulation rate on each of the three successive days it was determined. This might have been due to increase in the pleural fluid embarrassing the cardiac action or merely to diminution in the excitement caused by the manoeuvres. That the latter is probably the case is rendered likely by the lack of any appreciable rise in output after 27 ounces of fluid had been withdrawn from the left pleural cavity. There is no evidence therefore that in this case the pleural effusion had any effect on the cardiac output.

The second case was a woman with chronic nephritis and a high blood pressure. Her C.R. and S.V. are within normal limits while, since her oxygen absorption is extremely small, her oxygen utilization is low. It was hoped to observe in this patient the effect on the cardiac output of lowering the blood pressure by drugs of the nitrite series, but the fallacy, before mentioned, of repeated determinations rendered the results valueless.

L.M. Age 31. Female. Wt. 48.5. Pleurisy with Effusion.

Date.	Heart Rate per min.	Circ. Rate. Litres per min.	Stroke Volume c.c.	Stroke Index c.c. per kilo.	Resp. Volume Litres per min.	Alv. CO_2.	Oxygen Consumpt. c.c. per min.	R.Q.	Art. Ven. O_2 diff. Vols. per cent.	Remarks.
12.4.27	133	7.8	59	1.22	6.16	5.1%	270	.77	3.46	-
13.4.27	122	7.1	58	1.20	6.17	-	239	.80	3.37	-
14.4.27	126	5.8	46	.95	6.89	5.16%	260	.79	4.48	-
	Tapped ¾XXVIII fluid from left base.									
15.4.27	123	6.5	53	1.09	5.92	4.97%	220	.87	3.38	-
	Mrs B. Age 50. Wt. 45.5 Kg.					Chronic Interstitial Nephritis.				
4.2.27	85	5.5	65	1.43	3.10	5.44%	144	.9	2.62	-
1.2.27	82	6.3	77	1.69	3.39	5.55%	124	.87	1.94	-

CASE HISTORIES.

L.M.

Female. Age 31. Single. Domestic Servant.

Left sided pleural effusion up to 5th space, following acute pleurisy 6 weeks before admission. Probably tuberculous though this not definitely demonstrated.

Heart not displaced.

Diagnosis. Pleurisy with effusion.

Mrs B.

Age 50. Housewife.

Chronic interstitial nephritis apparently dating from Scarlet Fever associated with albuminuria at age of 5.

Hyperpiesis B.P. $\frac{200\text{-}300}{120\text{-}200}$ Vessel walls thickened.

Heart $\frac{111}{1''/4\frac{1}{4}''}$ in 5th L. space. Mitral systolic murmur. Accentuated aortic 2nd sound.

Diagnosis. Chronic Interstitial Nephritis.

S U M M A R Y.

1. Various methods used to determine the circulation rate are described, and the results obtained by them in health given and compared. From this it is concluded that

(a) the circulation rate in man may vary in health from 5-8 litres per minute and the stroke volume from 70-150 cc.

(b) the circulation depends on three variable factors, heart rate, stroke volume, and oxygen utilization, each of which is a potential reserve which may be called upon during exertion.

2. Circulation rates, determined by other observers, in various pathological states are given.

3. The technique of the ethyl iodide method is given and the validity of the method discussed.

4. The results of 215 observations on 26 patients suffering from various pathological conditions are given.

5. From these results and from those in (2) it is concluded that:-

(a) Valvular lesions, with the possible exception of advanced stenoses, have no direct effect on the cardiac output.

(b) Rapid irregular tachycardia, such as may occur in auricular fibrillation, reduces the circulation rate.

(c) In bradycardia due to complete heart block the output per beat is large. A practically normal resting circulation rate may be maintained.

(d) In advanced cardiac failure the circulation rate is low. In the ordinary types of cardiac failure this is due to the inability of the myocardium to maintain a sufficient output per beat, the rapid irregular tachycardia which may occur in auricular fibrillation being a probable contributory factor in these cases. It is suggested that the symptoms and signs of cardiac failure can be explained by the low circulation rate.

(e) Digitalis may increase, decrease, or leave unaffected the circulation rate. An increase is most likely to occur in the presence of a low circulation rate and definite signs of cardiac failure, but in such cases does not always occur. In cases with a moderate circulation rate and no marked signs of cardiac failure the circulation rate may be either unaffected or diminished. The probable cause of the variability of the effect of digitalis on the circulation rate is discussed.

(f)/

(f) In anaemia the circulation rate theoretically should be high, but in the cases examined the evidence that it is so is inconclusive. Probable reasons for this are discussed.

(g) The circulation rate tends to be high in exophthalmic goitre and low in myxoedema. In individual cases there is a definite degree of correlation between circulation rate and oxygen consumption.

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